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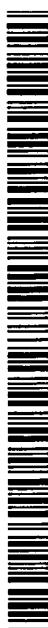
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(54) Title: COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF TUMOR

(57) Abstract: The present invention is directed to compositions of matter useful for the diagnosis and treatment of tumor in mammals and to methods of using those compositions of matter for the same.

COMPOSITIONS AND METHODS FOR THE DIAGNOSIS AND TREATMENT OF TUMOR

FIELD OF THE INVENTION

The present invention is directed to compositions of matter useful for the diagnosis and treatment of tumor in mammals and to methods of using those compositions of matter for the same.

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BACKGROUND OF THE INVENTION

Malignant tumors (cancers) are the second leading cause of death in the United States, after heart disease (Boring et al., *CA Cancel J. Clin.* 43:7 (1993)). Cancer is characterized by the increase in the number of abnormal, or neoplastic, cells derived from a normal tissue which proliferate to form a tumor mass, the 10 invasion of adjacent tissues by these neoplastic tumor cells, and the generation of malignant cells which eventually spread via the blood or lymphatic system to regional lymph nodes and to distant sites via a process called metastasis. In a cancerous state, a cell proliferates under conditions in which normal cells would not grow. Cancer manifests itself in a wide variety of forms, characterized by different degrees of invasiveness and aggressiveness.

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In attempts to discover effective cellular targets for cancer diagnosis and therapy, researchers have sought to identify transmembrane or otherwise membrane-associated polypeptides that are specifically expressed on the surface of one or more particular type(s) of cancer cell as compared to on one or more normal non-cancerous cell(s). Often, such membrane-associated polypeptides are more abundantly expressed on the surface of the cancer cells as compared to on the surface of the non-cancerous cells. The identification of such tumor-associated cell surface antigen polypeptides has given rise to the ability to specifically target cancer cells for destruction via antibody-based therapies. In this regard, it is noted that antibody-based therapy has proved very effective in the treatment of certain cancers. For example, HERCEPTIN® and RITUXAN® (both from Genentech Inc., South San Francisco, California) are antibodies that have been used successfully to treat breast cancer and non-Hodgkin's lymphoma, respectively. More specifically, HERCEPTIN® is a recombinant 20 DNA-derived humanized monoclonal antibody that selectively binds to the extracellular domain of the human epidermal growth factor receptor 2 (HER2) proto-oncogene. HER2 protein overexpression is observed in 25-30% of primary breast cancers. RITUXAN® is a genetically engineered chimeric murine/human monoclonal antibody directed against the CD20 antigen found on the surface of normal and malignant B lymphocytes. Both these antibodies are recombinantly produced in CHO cells.

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In other attempts to discover effective cellular targets for cancer diagnosis and therapy, researchers have sought to identify (1) non-membrane-associated polypeptides that are specifically produced by one or more particular type(s) of cancer cell(s) as compared to by one or more particular type(s) of non-cancerous normal cell(s), (2) polypeptides that are produced by cancer cells at an expression level that is significantly higher than that of one or more normal non-cancerous cell(s), or (3) polypeptides whose expression is specifically limited

to only a single (or very limited number of different) tissue type(s) in both the cancerous and non-cancerous state (e.g., normal prostate and prostate tumor tissue). Such polypeptides may remain intracellularly located or may be secreted by the cancer cell. Moreover, such polypeptides may be expressed not by the cancer cell itself, but rather by cells which produce and/or secrete polypeptides having a potentiating or growth-enhancing effect on cancer cells. Such secreted polypeptides are often proteins that provide cancer cells with a growth advantage over normal cells and include such things as, for example, angiogenic factors, cellular adhesion factors, growth factors, and the like. Identification of antagonists of such non-membrane associated polypeptides would be expected to serve as effective therapeutic agents for the treatment of such cancers. Furthermore, identification of the expression pattern of such polypeptides would be useful for the diagnosis of particular cancers in mammals.

Despite the above identified advances in mammalian cancer therapy, there is a great need for additional diagnostic and therapeutic agents capable of detecting the presence of tumor in a mammal and for effectively inhibiting neoplastic cell growth, respectively. Accordingly, it is an objective of the present invention to identify: (1) cell membrane-associated polypeptides that are more abundantly expressed on one or more type(s) of cancer cell(s) as compared to on normal cells or on other different cancer cells, (2) non-membrane-associated polypeptides that are specifically produced by one or more particular type(s) of cancer cell(s) (or by other cells that produce polypeptides having a potentiating effect on the growth of cancer cells) as compared to by one or more particular type(s) of non-cancerous normal cell(s), (3) non-membrane-associated polypeptides that are produced by cancer cells at an expression level that is significantly higher than that of one or more normal non-cancerous cell(s), or (4) polypeptides whose expression is specifically limited to only a single (or very limited number of different) tissue type(s) in both a cancerous and non-cancerous state (e.g., normal prostate and prostate tumor tissue), and to use those polypeptides, and their encoding nucleic acids, to produce compositions of matter useful in the therapeutic treatment and diagnostic detection of cancer in mammals. It is also an objective of the present invention to identify cell membrane-associated, secreted or intracellular polypeptides whose expression is limited to a single or very limited number of tissues, and to use those polypeptides, and their encoding nucleic acids, to produce compositions of matter useful in the therapeutic treatment and diagnostic detection of cancer in mammals.

SUMMARY OF THE INVENTION

A. Embodiments

In the present specification, Applicants describe for the first time the identification of various cellular polypeptides (and their encoding nucleic acids or fragments thereof) which are expressed to a greater degree on the surface of or by one or more types of cancer cell(s) as compared to on the surface of or by one or more types of normal non-cancer cells. Alternatively, such polypeptides are expressed by cells which produce and/or secrete polypeptides having a potentiating or growth-enhancing effect on cancer cells. Again alternatively, such polypeptides may not be overexpressed by tumor cells as compared to normal cells of the same tissue type, but rather may be specifically expressed by both tumor cells and normal cells of only a single or very limited

number of tissue types (preferably tissues which are not essential for life, e.g., prostate, etc.). All of the above polypeptides are herein referred to as Tumor-associated Antigenic Target polypeptides ("TAT" polypeptides) and are expected to serve as effective targets for cancer therapy and diagnosis in mammals.

Accordingly, in one embodiment of the present invention, the invention provides an isolated nucleic acid molecule having a nucleotide sequence that encodes a tumor-associated antigenic target polypeptide or fragment thereof (a "TAT" polypeptide).

In certain aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% nucleic acid sequence identity, to (a) a DNA molecule encoding a full-length TAT polypeptide having an amino acid sequence as disclosed herein, a TAT polypeptide amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane TAT polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In other aspects, the isolated nucleic acid molecule comprises a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% nucleic acid sequence identity, to (a) a DNA molecule comprising the coding sequence of a full-length TAT polypeptide cDNA as disclosed herein, the coding sequence of a TAT polypeptide lacking the signal peptide as disclosed herein, the coding sequence of an extracellular domain of a transmembrane TAT polypeptide, with or without the signal peptide, as disclosed herein or the coding sequence of any other specifically defined fragment of the full-length TAT polypeptide amino acid sequence as disclosed herein, or (b) the complement of the DNA molecule of (a).

In further aspects, the invention concerns an isolated nucleic acid molecule comprising a nucleotide sequence having at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% nucleic acid sequence identity, to (a) a DNA molecule that encodes the same mature polypeptide encoded by the full-length coding region of any of the human protein cDNAs deposited with the ATCC as disclosed herein, or (b) the complement of the DNA molecule of (a).

Another aspect of the invention provides an isolated nucleic acid molecule comprising a nucleotide sequence encoding a TAT polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated, or is complementary to such encoding nucleotide sequence, wherein the transmembrane domain(s) of such polypeptide(s) are disclosed herein. Therefore, soluble extracellular domains of the herein described TAT polypeptides are contemplated.

In other aspects, the present invention is directed to isolated nucleic acid molecules which hybridize to (a) a nucleotide sequence encoding a TAT polypeptide having a full-length amino acid sequence as disclosed herein, a TAT polypeptide amino acid sequence lacking the signal peptide as disclosed herein, an extracellular

domain of a transmembrane TAT polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide amino acid sequence as disclosed herein, or (b) the complement of the nucleotide sequence of (a). In this regard, an embodiment of the present invention is directed to fragments of a full-length TAT polypeptide coding sequence, or the complement thereof, as disclosed herein, that may find use as, for example, hybridization probes useful as, for example, diagnostic probes, antisense oligonucleotide probes, or for encoding fragments of a full-length TAT polypeptide that may 5 optionally encode a polypeptide comprising a binding site for an anti-TAT polypeptide antibody, a TAT binding oligopeptide or other small organic molecule that binds to a TAT polypeptide. Such nucleic acid fragments are usually at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 10 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, 15 wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length. It is noted that novel fragments of a TAT polypeptide-encoding nucleotide sequence may be determined in a routine manner by aligning the TAT polypeptide-encoding nucleotide sequence with other known nucleotide sequences using any of a number of well known sequence alignment programs and determining which TAT polypeptide-encoding nucleotide sequence fragment(s) are novel. All of such novel 20 fragments of TAT polypeptide-encoding nucleotide sequences are contemplated herein. Also contemplated are the TAT polypeptide fragments encoded by these nucleotide molecule fragments, preferably those TAT polypeptide fragments that comprise a binding site for an anti-TAT antibody, a TAT binding oligopeptide or other small organic molecule that binds to a TAT polypeptide.

In another embodiment, the invention provides isolated TAT polypeptides encoded by any of the 25 isolated nucleic acid sequences hereinabove identified.

In a certain aspect, the invention concerns an isolated TAT polypeptide, comprising an amino acid sequence having at least about 80% amino acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, 99% or 100% amino acid sequence identity, to a TAT polypeptide having a full-length amino acid sequence as disclosed herein, a 30 TAT polypeptide amino acid sequence lacking the signal peptide as disclosed herein, an extracellular domain of a transmembrane TAT polypeptide protein, with or without the signal peptide, as disclosed herein, an amino acid sequence encoded by any of the nucleic acid sequences disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide amino acid sequence as disclosed herein.

In a further aspect, the invention concerns an isolated TAT polypeptide comprising an amino acid 35 sequence having at least about 80% amino acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid

sequence identity, to an amino acid sequence encoded by any of the human protein cDNAs deposited with the ATCC as disclosed herein.

In a specific aspect, the invention provides an isolated TAT polypeptide without the N-terminal signal sequence and/or without the initiating methionine and is encoded by a nucleotide sequence that encodes such an amino acid sequence as hereinbefore described. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the TAT polypeptide and recovering the TAT polypeptide from the cell culture.

Another aspect of the invention provides an isolated TAT polypeptide which is either transmembrane domain-deleted or transmembrane domain-inactivated. Processes for producing the same are also herein described, wherein those processes comprise culturing a host cell comprising a vector which comprises the appropriate encoding nucleic acid molecule under conditions suitable for expression of the TAT polypeptide and recovering the TAT polypeptide from the cell culture.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described polypeptides. Host cells comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* cells, or yeast cells. A process for producing any of the herein described polypeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired polypeptide and recovering the desired polypeptide from the cell culture.

In other embodiments, the invention provides isolated chimeric polypeptides comprising any of the herein described TAT polypeptides fused to a heterologous (non-TAT) polypeptide. Example of such chimeric molecules comprise any of the herein described TAT polypeptides fused to a heterologous polypeptide such as, for example, an epitope tag sequence or a Fc region of an immunoglobulin.

In another embodiment, the invention provides an antibody which binds, preferably specifically, to any of the above or below described polypeptides. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, single-chain antibody or antibody that competitively inhibits the binding of an anti-TAT polypeptide antibody to its respective antigenic epitope. Antibodies of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies of the present invention may optionally be produced in CHO cells or bacterial cells and preferably induce death of a cell to which they bind. For diagnostic purposes, the antibodies of the present invention may be detectably labeled, attached to a solid support, or the like.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described antibodies. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* cells, or yeast cells. A process for producing any of the herein described antibodies is further provided and comprises culturing host cells under conditions suitable for expression of the desired antibody and recovering the desired antibody from the cell culture.

In another embodiment, the invention provides oligopeptides ("TAT binding oligopeptides") which

bind, preferably specifically, to any of the above or below described TAT polypeptides. Optionally, the TAT binding oligopeptides of the present invention may be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The TAT binding oligopeptides of the present invention may optionally be produced in CHO cells or bacterial cells and preferably induce death of a cell to which they bind. For 5 diagnostic purposes, the TAT binding oligopeptides of the present invention may be detectably labeled, attached to a solid support, or the like.

In other embodiments of the present invention, the invention provides vectors comprising DNA encoding any of the herein described TAT binding oligopeptides. Host cell comprising any such vector are also provided. By way of example, the host cells may be CHO cells, *E. coli* cells, or yeast cells. A process for 10 producing any of the herein described TAT binding oligopeptides is further provided and comprises culturing host cells under conditions suitable for expression of the desired oligopeptide and recovering the desired oligopeptide from the cell culture.

In another embodiment, the invention provides small organic molecules ("TAT binding organic molecules") which bind, preferably specifically, to any of the above or below described TAT polypeptides. 15 Optionally, the TAT binding organic molecules of the present invention may be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The TAT binding organic molecules of the present invention preferably induce death of a cell to which they bind. For diagnostic purposes, the TAT binding organic molecules of the present invention may be detectably labeled, attached to a solid support, or 20 the like.

In a still further embodiment, the invention concerns a composition of matter comprising a TAT polypeptide as described herein, a chimeric TAT polypeptide as described herein, an anti-TAT antibody as described herein, a TAT binding oligopeptide as described herein, or a TAT binding organic molecule as described herein, in combination with a carrier. Optionally, the carrier is a pharmaceutically acceptable carrier. 25

In yet another embodiment, the invention concerns an article of manufacture comprising a container and a composition of matter contained within the container, wherein the composition of matter may comprise a TAT polypeptide as described herein, a chimeric TAT polypeptide as described herein, an anti-TAT antibody as described herein, a TAT binding oligopeptide as described herein, or a TAT binding organic molecule as described herein. The article may further optionally comprise a label affixed to the container, or a package 30 insert included with the container, that refers to the use of the composition of matter for the therapeutic treatment or diagnostic detection of a tumor.

Another embodiment of the present invention is directed to the use of a TAT polypeptide as described herein, a chimeric TAT polypeptide as described herein, an anti-TAT polypeptide antibody as described herein, a TAT binding oligopeptide as described herein, or a TAT binding organic molecule as described herein, for 35 the preparation of a medicament useful in the treatment of a condition which is responsive to the TAT polypeptide, chimeric TAT polypeptide, anti-TAT polypeptide antibody, TAT binding oligopeptide, or TAT

binding organic molecule.

B. Additional Embodiments

Another embodiment of the present invention is directed to a method for inhibiting the growth of a cell that expresses a TAT polypeptide, wherein the method comprises contacting the cell with an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, and wherein the binding of the antibody, oligopeptide or organic molecule to the TAT polypeptide causes inhibition of the growth of the cell expressing the TAT polypeptide. In preferred embodiments, the cell is a cancer cell and binding of the antibody, oligopeptide or organic molecule to the TAT polypeptide causes death of the cell expressing the TAT polypeptide. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and TAT binding oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

Yet another embodiment of the present invention is directed to a method of therapeutically treating a mammal having a cancerous tumor comprising cells that express a TAT polypeptide, wherein the method comprises administering to the mammal a therapeutically effective amount of an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, thereby resulting in the effective therapeutic treatment of the tumor. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

Yet another embodiment of the present invention is directed to a method of determining the presence of a TAT polypeptide in a sample suspected of containing the TAT polypeptide, wherein the method comprises exposing the sample to an antibody, oligopeptide or small organic molecule that binds to the TAT polypeptide and determining binding of the antibody, oligopeptide or organic molecule to the TAT polypeptide in the sample, wherein the presence of such binding is indicative of the presence of the TAT polypeptide in the sample. Optionally, the sample may contain cells (which may be cancer cells) suspected of expressing the TAT polypeptide. The antibody, TAT binding oligopeptide or TAT binding organic molecule employed in the method may optionally be detectably labeled, attached to a solid support, or the like.

A further embodiment of the present invention is directed to a method of diagnosing the presence of a tumor in a mammal, wherein the method comprises detecting the level of expression of a gene encoding a TAT polypeptide (a) in a test sample of tissue cells obtained from said mammal, and (b) in a control sample of known normal non-cancerous cells of the same tissue origin or type, wherein a higher level of expression of the

TAT polypeptide in the test sample, as compared to the control sample, is indicative of the presence of tumor in the mammal from which the test sample was obtained.

Another embodiment of the present invention is directed to a method of diagnosing the presence of a tumor in a mammal, wherein the method comprises (a) contacting a test sample comprising tissue cells obtained from the mammal with an antibody, oligopeptide or small organic molecule that binds to a TAT polypeptide and (b) detecting the formation of a complex between the antibody, oligopeptide or small organic molecule and the TAT polypeptide in the test sample, wherein the formation of a complex is indicative of the presence of a tumor in the mammal. Optionally, the antibody, TAT binding oligopeptide or TAT binding organic molecule employed is detectably labeled, attached to a solid support, or the like, and/or the test sample of tissue cells is obtained from an individual suspected of having a cancerous tumor.

Yet another embodiment of the present invention is directed to a method for treating or preventing a cell proliferative disorder associated with altered, preferably increased, expression or activity of a TAT polypeptide, the method comprising administering to a subject in need of such treatment an effective amount of an antagonist of a TAT polypeptide. Preferably, the cell proliferative disorder is cancer and the antagonist of the TAT polypeptide is an anti-TAT polypeptide antibody, TAT binding oligopeptide, TAT binding organic molecule or antisense oligonucleotide. Effective treatment or prevention of the cell proliferative disorder may be a result of direct killing or growth inhibition of cells that express a TAT polypeptide or by antagonizing the cell growth potentiating activity of a TAT polypeptide.

Yet another embodiment of the present invention is directed to a method of binding an antibody, oligopeptide or small organic molecule to a cell that expresses a TAT polypeptide, wherein the method comprises contacting a cell that expresses a TAT polypeptide with said antibody, oligopeptide or small organic molecule under conditions which are suitable for binding of the antibody, oligopeptide or small organic molecule to said TAT polypeptide and allowing binding therebetween.

Other embodiments of the present invention are directed to the use of (a) a TAT polypeptide, (b) a nucleic acid encoding a TAT polypeptide or a vector or host cell comprising that nucleic acid, (c) an anti-TAT polypeptide antibody, (d) a TAT-binding oligopeptide, or (e) a TAT-binding small organic molecule in the preparation of a medicament useful for (i) the therapeutic treatment or diagnostic detection of a cancer or tumor, or (ii) the therapeutic treatment or prevention of a cell proliferative disorder.

Another embodiment of the present invention is directed to a method for inhibiting the growth of a cancer cell, wherein the growth of said cancer cell is at least in part dependent upon the growth potentiating effect(s) of a TAT polypeptide (wherein the TAT polypeptide may be expressed either by the cancer cell itself or a cell that produces polypeptide(s) that have a growth potentiating effect on cancer cells), wherein the method comprises contacting the TAT polypeptide with an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, thereby antagonizing the growth-potentiating activity of the TAT polypeptide and, in turn, inhibiting the growth of the cancer cell. Preferably the growth of the cancer cell is completely inhibited. Even more preferably, binding of the antibody, oligopeptide or small organic molecule to the TAT polypeptide induces the death of the cancer cell. Optionally, the antibody is a monoclonal antibody, antibody fragment,

chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and TAT binding oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

5 Yet another embodiment of the present invention is directed to a method of therapeutically treating a tumor in a mammal, wherein the growth of said tumor is at least in part dependent upon the growth potentiating effect(s) of a TAT polypeptide, wherein the method comprises administering to the mammal a therapeutically effective amount of an antibody, an oligopeptide or a small organic molecule that binds to the TAT polypeptide, thereby antagonizing the growth potentiating activity of said TAT polypeptide and resulting in the effective therapeutic treatment of the tumor. Optionally, the antibody is a monoclonal antibody, antibody fragment, chimeric antibody, humanized antibody, or single-chain antibody. Antibodies, TAT binding oligopeptides and TAT binding organic molecules employed in the methods of the present invention may optionally be conjugated to a growth inhibitory agent or cytotoxic agent such as a toxin, including, for example, a maytansinoid or calicheamicin, an antibiotic, a radioactive isotope, a nucleolytic enzyme, or the like. The antibodies and 10 oligopeptides employed in the methods of the present invention may optionally be produced in CHO cells or bacterial cells.

15 Yet further embodiments of the present invention will be evident to the skilled artisan upon a reading of the present specification.

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BRIEF DESCRIPTION OF THE DRAWINGS

In the list of figures for the present application, specific cDNA sequences which are upregulated in certain tumor tissues as compared to their normal tissue counterparts are individually identified with a designation beginning with the letters "DNA" followed by a specific numerical designation. A full or partial 25 length protein sequence that is encoded by a cDNA sequence identified and shown herein is individually identified with a designation beginning with the letters "PRO" followed by a specific numerical designation. Figures showing encoded amino acid sequences immediately follow the figure showing the cDNA sequence encoding that specific amino acid sequence. If start and/or stop codons have been identified in a cDNA sequence shown in the attached figures, they are shown in bold and underlined font.

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 Figure 50: DNA323741, NM_003132, gen.NM_003132
 Figure 51: PRO80498
 Figure 52: DNA323742, XM_086586, gen.XM_086586
 Figure 53: PRO80499
 Figure 54: DNA323743, XM_086587, gen.XM_086587
 Figure 55: DNA323744, XM_059230, gen.XM_059230
 Figure 56: PRO80501
 Figure 57A-B: DNA323745, XM_048780, gen.XM_048780
 Figure 58: DNA323746, XM_053183, gen.XM_053183
 Figure 59: DNA323747, XM_165442, gen.XM_165442
 Figure 60: DNA323748, NM_033440, gen.NM_033440
 Figure 61: PRO2269
 Figure 62: DNA323749, NM_024329, gen.NM_024329
 Figure 63: PRO80505
 Figure 64: DNA323750, XM_018205, gen.XM_018205
 Figure 65: PRO80506
 Figure 66: DNA323751, XM_011650, gen.XM_011650
 Figure 67: DNA323752, XM_017315, gen.XM_017315
 Figure 68A-B: DNA323753, XM_030470, gen.XM_030470
 Figure 69: DNA323754, NM_004930, gen.NM_004930
 Figure 70: PRO80510
 Figure 71: DNA323755, NM_003689, gen.NM_003689
 Figure 72: PRO80511
 Figure 73: DNA323756, NM_016183, gen.NM_016183
 Figure 74: PRO80512
 Figure 75: DNA323757, XM_015234, gen.XM_015234
 Figure 76A-B: DNA323758, XM_027916, gen.XM_027916
 Figure 77: DNA323759, XM_033683, gen.XM_033683
 Figure 78: DNA323760, XM_001826, gen.XM_001826
 Figure 79: DNA323761, XM_033654, gen.XM_033654
 Figure 80: PRO80517
 Figure 81: DNA323762, NM_001791, gen.NM_001791
 Figure 82: PRO26194
 Figure 83: DNA323763, NM_005826, gen.NM_005826
 Figure 84: PRO60815
 Figure 85: DNA323764, XM_086357, gen.XM_086357
 Figure 86: PRO80518
 Figure 87: DNA323765, NM_000975, gen.NM_000975
 Figure 88: PRO80519
 Figure 89: DNA323766, NM_007260, gen.NM_007260
 Figure 90: PRO61250
 Figure 91: DNA323767, NM_017761, gen.NM_017761
 Figure 92: PRO80520
 Figure 93: DNA323768, NM_006625, gen.NM_006625
 Figure 94: PRO22196
 Figure 95: DNA323769, NM_054016, gen.NM_054016
 Figure 96: PRO80521
 Figure 97: DNA323770, XM_086375, gen.XM_086375
 Figure 98: DNA323771, XM_006290, gen.XM_006290
 Figure 99: DNA323772, NM_015484, gen.NM_015484
 Figure 100: PRO80524
 Figure 101A-B: DNA323773, XM_001616, gen.XM_001616
 Figure 102: DNA323774, XM_058240,

gen.XM_058240
 Figure 103: DNA323775, XM_059117, gen.XM_059117
 Figure 104: PRO80527
 Figure 105: DNA226262, NM_005563, gen.NM_005563
 Figure 106: PRO36725
 Figure 107: DNA323776, NM_022778, gen.NM_022778
 Figure 108: PRO80528
 Figure 109: DNA323777, XM_017846, gen.XM_017846
 Figure 110: DNA323778, NM_005517, gen.NM_005517
 Figure 111: PRO80530
 Figure 112A-C: DNA323779, XM_046918, gen.XM_046918
 Figure 113: DNA323780, XM_002114, gen.XM_002114
 Figure 114: DNA323781, XM_059066, gen.XM_059066
 Figure 115: PRO80533
 Figure 116: DNA323782, NM_018066, gen.NM_018066
 Figure 117: PRO80534
 Figure 118: DNA323783, NM_006600, gen.NM_006600
 Figure 119: PRO80535
 Figure 120: DNA323784, XM_059067, gen.XM_059067
 Figure 121: PRO80536
 Figure 122: DNA323785, NM_032872, gen.NM_032872
 Figure 123: PRO80537
 Figure 124: DNA196349, NM_006990, gen.NM_006990
 Figure 125: PRO24856
 Figure 126: DNA323788, XM_001640, gen.XM_001640
 Figure 127: DNA323789, NM_002946, gen.NM_002946
 Figure 128: PRO59099
 Figure 129: DNA323790, XM_114044, gen.XM_114044
 Figure 130: DNA323791, XM_059088, gen.XM_059088
 Figure 131: DNA323792, NM_031459, gen.NM_031459
 Figure 132: PRO80542
 Figure 133: DNA323793, XM_010664, gen.XM_010664
 Figure 134: DNA323794, XM_001812, gen.XM_001812
 Figure 135: DNA323795, XM_001807, gen.XM_001807
 Figure 136: DNA323796, XM_086444, gen.XM_086444
 Figure 137: DNA323797, NM_024640, gen.NM_024640
 Figure 138: PRO80547
 Figure 139A-B: DNA323798, XM_049310, gen.XM_049310
 Figure 140: DNA323799, XM_113374, gen.XM_113374
 Figure 141: DNA323800, XM_002105, gen.XM_002105
 Figure 142: DNA323801, NM_014571, gen.NM_014571
 Figure 143: PRO80550
 Figure 144: DNA323802, XM_165438, gen.XM_165438
 Figure 145: DNA323803, XM_029844, gen.XM_029844
 Figure 146: DNA188748, NM_006559, gen.NM_006559
 Figure 147: PRO22304
 Figure 148: DNA323804, NM_003757, gen.NM_003757
 Figure 149: PRO80553
 Figure 150: DNA323805, NM_004964, gen.NM_004964
 Figure 151: PRO80554
 Figure 152: DNA323806, NM_023009, gen.NM_023009
 Figure 153: PRO80555
 Figure 154: DNA323807, XM_030423, gen.XM_030423
 Figure 155A-B: DNA323808, XM_036299, gen.XM_036299
 Figure 156: PRO80557
 Figure 157: DNA227213, NM_003680, gen.NM_003680
 Figure 158: PRO37676
 Figure 159: DNA323809, NM_006112, gen.NM_006112
 Figure 160: PRO80558
 Figure 161: DNA323810, XM_018136, gen.XM_018136
 Figure 162: PRO80559
 Figure 163: DNA323811, XM_117184, gen.XM_117184
 Figure 164: PRO80560
 Figure 165: DNA323812, NM_017825, gen.NM_017825
 Figure 166: PRO80561
 Figure 167: DNA189315, NM_014408, gen.NM_014408
 Figure 168: PRO22262
 Figure 169A-B: DNA323813, XM_029031, gen.XM_029031
 Figure 170: PRO80562
 Figure 171: DNA323814, XM_059171,

gen.XM_059171
Figure 172: PRO80563
Figure 173: DNA83085, NM_000760, gen.NM_000760
Figure 174: PRO2583
Figure 175: DNA323815, XM_165984, gen.XM_165984
Figure 176: DNA323816, XM_029842, gen.XM_029842
Figure 177: PRO2851
Figure 178: DNA323817, XM_086384, gen.XM_086384
Figure 179: PRO80565
Figure 180A-C: DNA274487, NM_014747, gen.NM_014747
Figure 181: PRO62389
Figure 182: DNA323818, XM_010712, gen.XM_010712
Figure 183: DNA323819, NM_024664, gen.NM_024664
Figure 184: PRO80567
Figure 185: DNA323820, XM_059214, gen.XM_059214
Figure 186: PRO80568
Figure 187: DNA323821, XM_046349, gen.XM_046349
Figure 188: DNA103253, NM_006516, gen.NM_006516
Figure 189: PRO4583
Figure 190: DNA323822, XM_086543, gen.XM_086543
Figure 191: PRO80570
Figure 192: DNA274745, NM_006824, gen.NM_006824
Figure 193: PRO62518
Figure 194: DNA273060, NM_001255, gen.NM_001255
Figure 195: PRO61125
Figure 196: DNA323823, NM_030587, gen.NM_030587
Figure 197: PRO80571
Figure 198: DNA323824, XM_097649, gen.XM_097649
Figure 199: DNA256503, NM_003780, gen.NM_003780
Figure 200: PRO51539
Figure 201: DNA323825, XM_046450, gen.XM_046450
Figure 202A-B: DNA272024, NM_014663, gen.NM_014663
Figure 203: PRO60298
Figure 204: DNA323826, XM_046565, gen.XM_046565
Figure 205: PRO80574
Figure 206: DNA323827, NM_024602, gen.NM_024602
Figure 207: PRO80575
Figure 208: DNA323828, XM_046557, gen.XM_046557
Figure 209: PRO80576
Figure 210: DNA323829, NM_001012, gen.NM_001012
Figure 211: PRO10760
Figure 212: DNA323830, XM_046551, gen.XM_046551
Figure 213A-B: DNA323831, XM_027983, gen.XM_027983
Figure 214: DNA323832, XM_086324, gen.XM_086324
Figure 215: PRO80579
Figure 216: DNA323833, XM_032391, gen.XM_032391
Figure 217: PRO80580
Figure 218: DNA103214, NM_006066, gen.NM_006066
Figure 219: PRO4544
Figure 220: DNA304686, NM_002574, gen.NM_002574
Figure 221: PRO71112
Figure 222: DNA323834, NM_032756, gen.NM_032756
Figure 223: PRO80581
Figure 224: DNA323835, XM_059133, gen.XM_059133
Figure 225: PRO80582
Figure 226: DNA323836, XM_027313, gen.XM_027313
Figure 227: PRO80583
Figure 228: DNA323837, XM_054868, gen.XM_054868
Figure 229: DNA323838, NM_001262, gen.NM_001262
Figure 230: PRO59546
Figure 231: DNA323839, XM_086391, gen.XM_086391
Figure 232: PRO80584
Figure 233: DNA323840, XM_114798, gen.XM_114798
Figure 234: PRO80585
Figure 235: DNA272748, NM_002979, gen.NM_002979
Figure 236: PRO60860
Figure 237: DNA323841, XM_038911, gen.XM_038911
Figure 238: PRO80586
Figure 239: DNA323842, NM_018070, gen.NM_018070
Figure 240: PRO80587
Figure 241: DNA323843, NM_024603, gen.NM_024603
Figure 242: PRO80588
Figure 243: DNA323844, XM_086389, gen.XM_086389

Figure 244: DNA323845, XM_038852, gen.XM_038852
Figure 245: DNA323846, NM_032864, gen.NM_032864
Figure 246: PRO80591
Figure 247: DNA323847, NM_024586, gen.NM_024586
Figure 248: PRO80592
Figure 249A-B: DNA323848, XM_097565, gen.XM_097565
Figure 250: DNA323849, XM_001472, gen.XM_001472
Figure 251A-C: DNA323850, XM_055481, gen.XM_055481
Figure 252: PRO80593
Figure 253: DNA323851, XM_010615, gen.XM_010615
Figure 254A-B: DNA323852, XM_089138, gen.XM_089138
Figure 255: PRO80595
Figure 256A-B: DNA323853, XM_059180, gen.XM_059180
Figure 257: DNA323854, XM_015717, gen.XM_015717
Figure 258: PRO80597
Figure 259: DNA323855, XM_114125, gen.XM_114125
Figure 260: DNA323856, NM_015640, gen.NM_015640
Figure 261: PRO80599
Figure 262: DNA323857, NM_017768, gen.NM_017768
Figure 263: PRO80600
Figure 264: DNA323858, XM_165977, gen.XM_165977
Figure 265: DNA323859, XM_086343, gen.XM_086343
Figure 266: PRO80602
Figure 267: DNA269708, NM_007034, gen.NM_007034
Figure 268: PRO58118
Figure 269: DNA323860, NM_001554, gen.NM_001554
Figure 270: PRO80603
Figure 271: DNA226260, NM_006769, gen.NM_006769
Figure 272: PRO36723
Figure 273: DNA323861, NM_004261, gen.NM_004261
Figure 274: PRO80604
Figure 275: DNA323862, XM_165983, gen.XM_165983
Figure 276: DNA323863, XM_016164, gen.XM_016164
Figure 277: DNA323864, XM_086164, gen.XM_086164

Figure 278: PRO80607
Figure 279: DNA323865, XM_086165, gen.XM_086165
Figure 280: DNA323866, XM_086167, gen.XM_086167
Figure 281: DNA323867, XM_086166, gen.XM_086166
Figure 282: DNA323868, XM_086138, gen.XM_086138
Figure 283: PRO80611
Figure 284: DNA323869, NM_000969, gen.NM_000969
Figure 285: PRO80612
Figure 286: DNA323870, XM_088863, gen.XM_088863
Figure 287: PRO80613
Figure 288: DNA271003, NM_003729, gen.NM_003729
Figure 289: PRO59332
Figure 290: DNA323871, XM_165981, gen.XM_165981
Figure 291: PRO80614
Figure 292: DNA275139, NM_013296, gen.NM_013296
Figure 293: PRO62849
Figure 294: DNA323872, XM_058702, gen.XM_058702
Figure 295: DNA323873, XM_054978, gen.XM_054978
Figure 296: DNA323874, NM_032636, gen.NM_032636
Figure 297: PRO80617
Figure 298: DNA323875, NM_006513, gen.NM_006513
Figure 299: PRO80618
Figure 300: DNA323876, NM_006621, gen.NM_006621
Figure 301: PRO80619
Figure 302A-B: DNA323877, NM_007158, gen.NM_007158
Figure 303: PRO80620
Figure 304: DNA323878, XM_086132, gen.XM_086132
Figure 305: PRO80621
Figure 306: DNA323879, NM_004000, gen.NM_004000
Figure 307: PRO80622
Figure 308: DNA323880, NM_001688, gen.NM_001688
Figure 309: PRO80623
Figure 310: DNA323881, NM_019099, gen.NM_019099
Figure 311: PRO80624
Figure 312A-B: DNA323882, NM_000701, gen.NM_000701
Figure 313: PRO80625

Figure 314A-B: DNA323883, XM_018332, gen.XM_018332
Figure 315A-B: DNA323884, XM_040709, gen.XM_040709
Figure 316: PRO80627
Figure 317: DNA323885, XM_086518, gen.XM_086518
Figure 318A-D: DNA323886, XM_034671, gen.XM_034671
Figure 319: DNA323887, XM_034662, gen.XM_034662
Figure 320: PRO80630
Figure 321: DNA323888, XM_039721, gen.XM_039721
Figure 322: PRO80631
Figure 323A-B: DNA323889, XM_086397, gen.XM_086397
Figure 324A-B: DNA323890, XM_086515, gen.XM_086515
Figure 325: PRO80633
Figure 326: DNA323891, XM_016480, gen.XM_016480
Figure 327: DNA323892, XM_165975, gen.XM_165975
Figure 328: DNA323893, NM_016361, gen.NM_016361
Figure 329: PRO231
Figure 330: DNA323894, XM_059210, gen.XM_059210
Figure 331: DNA323895, XM_086296, gen.XM_086296
Figure 332: DNA323896, NM_030920, gen.NM_030920
Figure 333: PRO80638
Figure 334: DNA323897, NM_016022, gen.NM_016022
Figure 335: PRO80639
Figure 336: DNA323898, NM_031901, gen.NM_031901
Figure 337: PRO80640
Figure 338A-B: DNA323899, XM_088788, gen.XM_088788
Figure 339: PRO80641
Figure 340: DNA274759, NM_005620, gen.NM_005620
Figure 341: PRO62529
Figure 342: DNA323900, XM_001468, gen.XM_001468
Figure 343: PRO49642
Figure 344: DNA323901, NM_006862, gen.NM_006862
Figure 345: PRO80642
Figure 346: DNA227529, NM_002796, gen.NM_002796
Figure 347: PRO37992
Figure 348: DNA323902, NM_002810, gen.NM_002810
Figure 349: PRO61638
Figure 350: DNA290284, NM_005997, gen.NM_005997
Figure 351: PRO70433
Figure 352: DNA323903, XM_097639, gen.XM_097639
Figure 353: DNA323904, XM_041879, gen.XM_041879
Figure 354: DNA323905, XM_041884, gen.XM_041884
Figure 355: PRO80644
Figure 356: DNA225809, NM_000396, gen.NM_000396
Figure 357: PRO36272
Figure 358: DNA323906, NM_025150, gen.NM_025150
Figure 359: PRO80645
Figure 360: DNA323907, XM_114098, gen.XM_114098
Figure 361: DNA323908, XM_113369, gen.XM_113369
Figure 362: PRO80646
Figure 363: DNA323909, XM_099467, gen.XM_099467
Figure 364: DNA323910, NM_002965, gen.NM_002965
Figure 365: PRO80648
Figure 366: DNA323911, XM_086400, gen.XM_086400
Figure 367: DNA210134, NM_014624, gen.NM_014624
Figure 368: PRO33679
Figure 369: DNA304666, NM_002961, gen.NM_002961
Figure 370: PRO71093
Figure 371: DNA304720, NM_019554, gen.NM_019554
Figure 372: PRO71146
Figure 373: DNA323912, XM_165976, gen.XM_165976
Figure 374: DNA227577, NM_006271, gen.NM_006271
Figure 375: PRO38040
Figure 376: DNA323913, XM_114097, gen.XM_114097
Figure 377: DNA323914, XM_040009, gen.XM_040009
Figure 378: PRO80651
Figure 379: DNA323915, NM_024330, gen.NM_024330
Figure 380: PRO703
Figure 381: DNA323916, NM_012437, gen.NM_012437
Figure 382: PRO80652
Figure 383: DNA323917, XM_086271,

gen.XM_086271
Figure 384: DNA323918, XM_114055, gen.XM_114055
Figure 385: PRO37535
Figure 386: DNA323919, XM_113360, gen.XM_113360
Figure 387: PRO80654
Figure 388: DNA323920, XM_086564, gen.XM_086564
Figure 389: DNA323921, NM_005973, gen.NM_005973
Figure 390: PRO80656
Figure 391: DNA323922, XM_044077, gen.XM_044077
Figure 392: DNA323923, NM_001878, gen.NM_001878
Figure 393: PRO80657
Figure 394: DNA323924, NM_021948, gen.NM_021948
Figure 395: PRO6018
Figure 396: DNA273088, NM_006365, gen.NM_006365
Figure 397: PRO61146
Figure 398: DNA323925, XM_044127, gen.XM_044127
Figure 399: PRO80658
Figure 400: DNA323926, XM_053245, gen.XM_053245
Figure 401: PRO80659
Figure 402: DNA257916, NM_032323, gen.NM_032323
Figure 403: PRO52449
Figure 404: DNA323927, NM_005572, gen.NM_005572
Figure 405: PRO80660
Figure 406: DNA323928, XM_044166, gen.XM_044166
Figure 407: PRO80661
Figure 408: DNA323929, XM_044128, gen.XM_044128
Figure 409: DNA226125, NM_003145, gen.NM_003145
Figure 410: PRO36588
Figure 411A-B: DNA323930, XM_044172, gen.XM_044172
Figure 412: DNA323931, NM_032292, gen.NM_032292
Figure 413: PRO80664
Figure 414: DNA323932, NM_004632, gen.NM_004632
Figure 415: PRO80665
Figure 416: DNA323933, XM_044075, gen.XM_044075
Figure 417: PRO80666
Figure 418: DNA323934, NM_018253, gen.NM_018253
Figure 419: PRO80667
Figure 420: DNA323935, NM_018116, gen.NM_018116
Figure 421: PRO80668
Figure 422: DNA323936, NM_002004, gen.NM_002004
Figure 423: PRO80669
Figure 424: DNA323937, NM_005698, gen.NM_005698
Figure 425: PRO80670
Figure 426: DNA323938, NM_052837, gen.NM_052837
Figure 427: PRO80671
Figure 428: DNA194600, NM_006589, gen.NM_006589
Figure 429: PRO23942
Figure 430: DNA323939, XM_086567, gen.XM_086567
Figure 431: PRO80672
Figure 432: DNA323940, XM_086552, gen.XM_086552
Figure 433: DNA323941, XM_036744, gen.XM_036744
Figure 434: DNA323942, NM_130898, gen.NM_130898
Figure 435: PRO80675
Figure 436: DNA226793, NM_006694, gen.NM_006694
Figure 437: PRO37256
Figure 438: DNA294794, NM_002870, gen.NM_002870
Figure 439: PRO70754
Figure 440: DNA323943, NM_001030, gen.NM_001030
Figure 441: PRO80676
Figure 442: DNA323944, XM_036829, gen.XM_036829
Figure 443: PRO80677
Figure 444: DNA323945, NM_015449, gen.NM_015449
Figure 445: PRO80678
Figure 446: DNA323946, NM_014847, gen.NM_014847
Figure 447: PRO80679
Figure 448: DNA323947, XM_036934, gen.XM_036934
Figure 449: PRO80680
Figure 450A-B: DNA323948, XM_036845, gen.XM_036845
Figure 451: DNA323949, XM_010636, gen.XM_010636
Figure 452: DNA323950, NM_006556, gen.NM_006556
Figure 453: PRO62574
Figure 454: DNA323951, XM_034082, gen.XM_034082

Figure 455: DNA323952, NM_025207, gen.NM_025207
Figure 456: PRO80684
Figure 457: DNA103436, NM_003815, gen.NM_003815
Figure 458: PRO4763
Figure 459: DNA323953, NM_003516, gen.NM_003516
Figure 460: PRO80685
Figure 461: DNA323954, NM_005850, gen.NM_005850
Figure 462: PRO59725
Figure 463A-B: DNA323955, NM_014849, gen.NM_014849
Figure 464: PRO80686
Figure 465: DNA323956, XM_059094, gen.XM_059094
Figure 466: DNA323957, XM_058247, gen.XM_058247
Figure 467: PRO80688
Figure 468: DNA323958, NM_003779, gen.NM_003779
Figure 469: PRO80689
Figure 470: DNA323959, NM_004550, gen.NM_004550
Figure 471: PRO58974
Figure 472: DNA323960, XM_085581, gen.XM_085581
Figure 473: DNA323961, XM_113379, gen.XM_113379
Figure 474: DNA226619, NM_003564, gen.NM_003564
Figure 475: PRO37082
Figure 476A-B: DNA323962, XM_049680, gen.XM_049680
Figure 477: DNA323963, XM_165443, gen.XM_165443
Figure 478: PRO80693
Figure 479: DNA323964, XM_086381, gen.XM_086381
Figure 480: PRO80694
Figure 481A-B: DNA323965, NM_002857, gen.NM_002857
Figure 482: PRO80695
Figure 483A-B: DNA323966, XM_049690, gen.XM_049690
Figure 484: DNA323967, XM_114153, gen.XM_114153
Figure 485: DNA323968, XM_086378, gen.XM_086378
Figure 486: DNA323969, XM_001897, gen.XM_001897
Figure 487: PRO10002
Figure 488: DNA323970, NM_052862, gen.NM_052862
Figure 489: PRO80699

Figure 490: DNA323971, XM_086481, gen.XM_086481
Figure 491: PRO80700
Figure 492: DNA323972, XM_059191, gen.XM_059191
Figure 493: DNA323973, XM_086485, gen.XM_086485
Figure 494: DNA323974, XM_086484, gen.XM_086484
Figure 495: DNA323975, XM_047479, gen.XM_047479
Figure 496: PRO80704
Figure 497: DNA323976, NM_003617, gen.NM_003617
Figure 498: PRO37806
Figure 499: DNA254298, NM_025226, gen.NM_025226
Figure 500: PRO49409
Figure 501: DNA323977, XM_034000, gen.XM_034000
Figure 502: PRO80705
Figure 503: DNA323978, NM_032738, gen.NM_032738
Figure 504: PRO329
Figure 505: DNA323979, NM_000569, gen.NM_000569
Figure 506: PRO80706
Figure 507: DNA323980, XM_088945, gen.XM_088945
Figure 508: PRO80707
Figure 509: DNA323981, XM_060331, gen.XM_060331
Figure 510: PRO80708
Figure 511: DNA323982, NM_004905, gen.NM_004905
Figure 512: PRO80709
Figure 513: DNA323983, NM_017847, gen.NM_017847
Figure 514: PRO80710
Figure 515A-B: DNA323984, XM_051877, gen.XM_051877
Figure 516: PRO62077
Figure 517: DNA323985, NM_005717, gen.NM_005717
Figure 518: PRO80711
Figure 519A-B: DNA271986, NM_014837, gen.NM_014837
Figure 520: PRO60261
Figure 521A-B: DNA323986, XM_056923, gen.XM_056923
Figure 522: DNA323987, XM_046464, gen.XM_046464
Figure 523: DNA323988, XM_002068, gen.XM_002068
Figure 524A-B: DNA323989, XM_001289, gen.XM_001289

Figure 525: DNA323990, XM_114109, gen.XM_114109
Figure 526: PRO80714
Figure 527: DNA323991, NM_022371, gen.NM_022371
Figure 528: PRO80715
Figure 529: DNA323992, NM_004673, gen.NM_004673
Figure 530: PRO188
Figure 531: DNA323993, XM_060517, gen.XM_060517
Figure 532: DNA323994, XM_165978, gen.XM_165978
Figure 533: PRO80717
Figure 534: DNA323995, XM_117181, gen.XM_117181
Figure 535: DNA323996, NM_018122, gen.NM_018122
Figure 536: PRO80719
Figure 537: DNA323997, XM_042967, gen.XM_042967
Figure 538: DNA323998, XM_086494, gen.XM_086494
Figure 539: PRO80720
Figure 540: DNA290234, NM_002923, gen.NM_002923
Figure 541: PRO70333
Figure 542: DNA323999, XM_086328, gen.XM_086328
Figure 543: DNA324000, XM_086282, gen.XM_086282
Figure 544: DNA324001, XM_053633, gen.XM_053633
Figure 545: DNA256905, NM_138391, gen.NM_138391
Figure 546: PRO51836
Figure 547: DNA324002, XM_015434, gen.XM_015434
Figure 548: DNA324003, NM_006763, gen.NM_006763
Figure 549: PRO80725
Figure 550: DNA227246, NM_005686, gen.NM_005686
Figure 551: PRO37709
Figure 552: DNA324004, XM_058405, gen.XM_058405
Figure 553A-B: DNA226005, NM_000228, gen.NM_000228
Figure 554: PRO36468
Figure 555: DNA324005, NM_015714, gen.NM_015714
Figure 556: PRO11582
Figure 557: DNA324006, XM_086142, gen.XM_086142
Figure 558: DNA83046, NM_000574, gen.NM_000574
Figure 559: PRO2569
Figure 560A-B: DNA324007, XM_114030, gen.XM_114030
Figure 561: DNA324008, XM_097519, gen.XM_097519
Figure 562: DNA324009, XM_059120, gen.XM_059120
Figure 563: PRO80730
Figure 564: DNA324010, NM_016456, gen.NM_016456
Figure 565: PRO1248
Figure 566: DNA324011, XM_036556, gen.XM_036556
Figure 567: DNA324012, XM_001914, gen.XM_001914
Figure 568: DNA324013, XM_001916, gen.XM_001916
Figure 569: DNA324014, NM_018085, gen.NM_018085
Figure 570: PRO80734
Figure 571: DNA324015, NM_006335, gen.NM_006335
Figure 572: PRO80735
Figure 573: DNA324016, XM_036500, gen.XM_036500
Figure 574: PRO80736
Figure 575: DNA324017, XM_036507, gen.XM_036507
Figure 576: DNA196344, NM_004767, gen.NM_004767
Figure 577: PRO24851
Figure 578: DNA247474, NM_014176, gen.NM_014176
Figure 579: PRO44999
Figure 580A-B: DNA324018, XM_084055, gen.XM_084055
Figure 581: DNA324019, XM_010682, gen.XM_010682
Figure 582: DNA324020, XM_117185, gen.XM_117185
Figure 583: DNA324021, XM_055880, gen.XM_055880
Figure 584: PRO80740
Figure 585: DNA193882, NM_014184, gen.NM_014184
Figure 586: PRO23300
Figure 587: DNA324022, NM_018212, gen.NM_018212
Figure 588: PRO80741
Figure 589: DNA324023, XM_086431, gen.XM_086431
Figure 590: PRO80742
Figure 591: DNA324024, XM_037329, gen.XM_037329
Figure 592: DNA324025, XM_086432, gen.XM_086432
Figure 593A-B: DNA324026, XM_010732,

gen.XM_010732
 Figure 594: DNA227504, NM_000447, gen.NM_000447
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 Figure 596: DNA324027, NM_012486, gen.NM_012486
 Figure 597: PRO80745
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 Figure 599A-B: DNA324029, XM_001958, gen.XM_001958
 Figure 600: DNA324030, XM_016199, gen.XM_016199
 Figure 601: DNA324031, XM_086244, gen.XM_086244
 Figure 602: DNA324032, XM_086245, gen.XM_086245
 Figure 603: DNA254346, NM_024709, gen.NM_024709
 Figure 604: PRO49457
 Figure 605: DNA324033, XM_088107, gen.XM_088107
 Figure 606: DNA324034, NM_032890, gen.NM_032890
 Figure 607: PRO80752
 Figure 608: DNA324035, XM_052974, gen.XM_052974
 Figure 609: PRO80753
 Figure 610: DNA324036, XM_047499, gen.XM_047499
 Figure 611: PRO80754
 Figure 612: DNA324037, NM_000858, gen.NM_000858
 Figure 613: PRO80755
 Figure 614: DNA324038, NM_024319, gen.NM_024319
 Figure 615: PRO80756
 Figure 616: DNA324039, XM_047545, gen.XM_047545
 Figure 617: PRO4914
 Figure 618A-B: DNA324040, XM_056884, gen.XM_056884
 Figure 619: DNA324041, XM_098599, gen.XM_098599
 Figure 620: DNA324042, XM_165439, gen.XM_165439
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 Figure 624: DNA82328, NM_000029, gen.NM_000029
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 Figure 629: PRO80762
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 Figure 631: PRO80763
 Figure 632: DNA324047, XM_086257, gen.XM_086257
 Figure 633: PRO80764
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 Figure 636: DNA324049, NM_000143, gen.NM_000143
 Figure 637: PRO62607
 Figure 638: DNA324050, XM_090833, gen.XM_090833
 Figure 639: DNA324051, NM_130398, gen.NM_130398
 Figure 640: PRO80767
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 Figure 642: DNA324053, XM_018041, gen.XM_018041
 Figure 643: DNA324054, NM_001011, gen.NM_001011
 Figure 644: PRO10692
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 Figure 646: PRO1182
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 Figure 649: DNA103217, NM_003310, gen.NM_003310
 Figure 650: PRO4547
 Figure 651: DNA275195, NM_001034, gen.NM_001034
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 Figure 653: DNA324057, XM_059368, gen.XM_059368
 Figure 654: PRO80771
 Figure 655: DNA324058, NM_006826, gen.NM_006826
 Figure 656: PRO70258
 Figure 657: DNA324059, NM_005378, gen.NM_005378
 Figure 658: PRO80772
 Figure 659: DNA324060, NM_002539, gen.NM_002539
 Figure 660: PRO80773
 Figure 661: DNA324061, XM_096149, gen.XM_096149
 Figure 662: DNA275049, NM_004939, gen.NM_004939
 Figure 663: PRO62770
 Figure 664A-B: DNA324062, XM_036450,

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 Figure 665: DNA324063, XM_103946,
 gen.XM_103946
 Figure 666: PRO80775
 Figure 667: DNA324064, NM_014713,
 gen.NM_014713
 Figure 668: PRO80776
 Figure 669: DNA324065, XM_087206,
 gen.XM_087206
 Figure 670: DNA324066, NM_106552,
 gen.NM_106552
 Figure 671: PRO80778
 Figure 672: DNA324067, XM_092135,
 gen.XM_092135
 Figure 673: PRO80779
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 gen.NM_017910
 Figure 675: PRO80780
 Figure 676: DNA324069, XM_092517,
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 Figure 680: DNA324071, XM_002480,
 gen.XM_002480
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 Figure 683: DNA324073, XM_087151,
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 Figure 692A-B: DNA324076, NM_004341,
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 gen.NM_016085
 Figure 695: PRO80788
 Figure 696: DNA324078, NM_080592,
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 Figure 701: DNA324080, NM_000221,
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 Figure 702: PRO80790
 Figure 703: DNA271243, NM_006488,
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 Figure 704: PRO59558
 Figure 705: DNA324081, NM_007046,
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 Figure 706: PRO9886
 Figure 707: DNA324082, NM_021831,
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 Figure 708: PRO80791
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 Figure 710: PRO80792
 Figure 711: DNA103593, NM_000183,
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 Figure 727: DNA324093, NM_138801,
 gen.NM_138801
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 Figure 748: DNA324102, XM_087051, gen.XM_087051
 Figure 749: DNA324103, NM_002954, gen.NM_002954
 Figure 750: PRO62239
 Figure 751: DNA271060, NM_002453, gen.NM_002453
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 Figure 804: PRO37991

Figure 805: DNA324134, XM_086920, gen.XM_086920

Figure 806: DNA150725, NM_001747, gen.NM_001747

Figure 807: PRO12792

Figure 808: DNA324135, NM_005911, gen.NM_005911

Figure 809: PRO80837

Figure 810: DNA324136, NM_032827, gen.NM_032827

Figure 811: PRO80838

Figure 812: DNA324137, NM_017952, gen.NM_017952

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Figure 816: DNA324138, XM_114215, gen.XM_114215

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Figure 819: PRO80842

Figure 820A-B: DNA324141, XM_049108, gen.XM_049108

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Figure 822: DNA324142, XM_049113, gen.XM_049113

Figure 823: DNA324143, XM_002611, gen.XM_002611

Figure 824A-B: DNA324144, XM_114247, gen.XM_114247

Figure 825: DNA324145, NM_017789, gen.NM_017789

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Figure 827: DNA324146, NM_001862, gen.NM_001862

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Figure 831A-B: DNA324148, XM_037108, gen.XM_037108

Figure 832: DNA324149, NM_000993, gen.NM_000993

Figure 833: PRO11197

Figure 834: DNA324150, NM_017546, gen.NM_017546

Figure 835: PRO80850

Figure 836: DNA324151, NM_001450, gen.NM_001450

Figure 837: PRO80851

Figure 838: DNA324152, XM_114229, gen.XM_114229

Figure 839: DNA324153, XM_087122, gen.XM_087122

Figure 840: PRO80853

Figure 841: DNA324154, XM_018540, gen.XM_018540

Figure 842: DNA324155, XM_087040, gen.XM_087040

Figure 843: DNA324156, NM_032212, gen.NM_032212

Figure 844: PRO80856

Figure 845: DNA324157, XM_002217, gen.XM_002217

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Figure 847: DNA324158, NM_000576, gen.NM_000576

Figure 848: PRO65

Figure 849: DNA324159, XM_086923, gen.XM_086923

Figure 850: DNA324160, XM_086925, gen.XM_086925

Figure 851A-B: DNA324161, XM_114266, gen.XM_114266

Figure 852: PRO80860

Figure 853: DNA324162, XM_002704, gen.XM_002704

Figure 854: DNA194740, NM_005291, gen.NM_005291

Figure 855: PRO24028

Figure 856A-B: DNA324163, XM_114267, gen.XM_114267

Figure 857: DNA324164, XM_034952, gen.XM_034952

Figure 858: DNA324165, XM_086950, gen.XM_086950

Figure 859A-B: DNA255531, NM_017751, gen.NM_017751

Figure 860: PRO50596

Figure 861: DNA324166, XM_017698, gen.XM_017698

Figure 862: DNA324167, XM_030529, gen.XM_030529

Figure 863: PRO80866

Figure 864: DNA275240, NM_005915, gen.NM_005915

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Figure 867: DNA324169, XM_092489, gen.XM_092489

Figure 868: PRO80868

Figure 869: DNA324170, XM_115672, gen.XM_115672

Figure 870: PRO80869

Figure 871: DNA324171, NM_020548, gen.NM_020548

Figure 872: PRO60753

Figure 873: DNA324172, XM_037101,

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Figure 875: DNA324173, NM_032390, gen.NM_032390
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Figure 888: PRO80877
Figure 889: DNA324180, NM_016839, gen.NM_016839
Figure 890: PRO80878
Figure 891: DNA324181, XM_087118, gen.XM_087118
Figure 892: PRO80879
Figure 893: DNA324182, XM_165998, gen.XM_165998
Figure 894: DNA324183, NM_001935, gen.NM_001935
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Figure 900: DNA324185, XM_166008, gen.XM_166008
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Figure 928: DNA324202, XM_045170, gen.XM_045170
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Figure 942: DNA324210, XM_087028, gen.XM_087028

Figure 943: PRO80903
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Figure 979: DNA324230, XM_050638, gen.XM_050638
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 Figure 993: DNA324239, XM_087166, gen.XM_087166
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 Figure 998: DNA189697, NM_004846, gen.NM_004846
 Figure 999: PRO23123
 Figure 1000: DNA324241, NM_025202, gen.NM_025202
 Figure 1001: PRO80925
 Figure 1002: DNA324242, XM_115825, gen.XM_115825
 Figure 1003: PRO80926
 Figure 1004: DNA324243, XM_010858, gen.XM_010858
 Figure 1005: PRO80927
 Figure 1006: DNA324244, XM_002540, gen.XM_002540
 Figure 1007: DNA324245, XM_048690, gen.XM_048690
 Figure 1008: PRO80929
 Figure 1009: DNA324246, NM_030926, gen.NM_030926
 Figure 1010: PRO80930
 Figure 1011: DNA324247, XM_087218, gen.XM_087218
 Figure 1012: DNA324248, NM_004509, gen.NM_004509
 Figure 1013: PRO80932

Figure 1014: DNA324249, NM_004510, gen.NM_004510
Figure 1015: PRO80933
Figure 1016: DNA324250, NM_080424, gen.NM_080424
Figure 1017: PRO80934
Figure 1018: DNA324251, NM_018410, gen.NM_018410
Figure 1019: PRO80935
Figure 1020: DNA324252, NM_017974, gen.NM_017974
Figure 1021: PRO80936
Figure 1022A-B: DNA324253, XM_096169, gen.XM_096169
Figure 1023: PRO80937
Figure 1024: DNA150884, NM_005855, gen.NM_005855
Figure 1025: PRO12520
Figure 1026A-B: DNA324254, NM_004735, gen.NM_004735
Figure 1027: PRO80938
Figure 1028A-C: DNA324255, XM_030203, gen.XM_030203
Figure 1029: DNA324256, XM_059372, gen.XM_059372
Figure 1030: DNA324257, NM_002712, gen.NM_002712
Figure 1031: PRO80941
Figure 1032A-B: DNA324258, XM_042326, gen.XM_042326
Figure 1033: PRO80942
Figure 1034: DNA324259, NM_004404, gen.NM_004404
Figure 1035: PRO80943
Figure 1036: DNA324260, XM_002742, gen.XM_002742
Figure 1037: DNA324261, NM_138483, gen.NM_138483
Figure 1038: PRO80945
Figure 1039: DNA324262, XM_115706, gen.XM_115706
Figure 1040: DNA324263, XM_115722, gen.XM_115722
Figure 1041: DNA324264, XM_084141, gen.XM_084141
Figure 1042: DNA324265, XM_005086, gen.XM_005086
Figure 1043: DNA324266, NM_015453, gen.NM_015453
Figure 1044: PRO80949
Figure 1045: DNA324267, NM_022485, gen.NM_022485
Figure 1046: PRO80950
Figure 1047A-B: DNA324268, XM_054520, gen.XM_054520
Figure 1048: PRO80951

Figure 1049: DNA324269, NM_006354, gen.NM_006354
Figure 1050: PRO80952
Figure 1051: DNA324270, NM_133480, gen.NM_133480
Figure 1052: PRO80953
Figure 1053: DNA324271, NM_133481, gen.NM_133481
Figure 1054: PRO80954
Figure 1055: DNA324272, NM_005718, gen.NM_005718
Figure 1056: PRO80955
Figure 1057: DNA324273, NM_015644, gen.NM_015644
Figure 1058: PRO80956
Figure 1059: DNA324274, XM_059561, gen.XM_059561
Figure 1060: DNA324275, XM_052310, gen.XM_052310
Figure 1061: PRO80958
Figure 1062: DNA269910, NM_006395, gen.NM_006395
Figure 1063: PRO58308
Figure 1064: DNA324276, NM_000994, gen.NM_000994
Figure 1065: PRO80959
Figure 1066: DNA151017, NM_004844, gen.NM_004844
Figure 1067: PRO12841
Figure 1068: DNA324277, XM_059557, gen.XM_059557
Figure 1069: PRO80960
Figure 1070A-B: DNA324278, XM_042860, gen.XM_042860
Figure 1071: PRO80961
Figure 1072: DNA324279, XM_042841, gen.XM_042841
Figure 1073: PRO80962
Figure 1074: DNA324280, XM_053712, gen.XM_053712
Figure 1075: DNA324281, XM_087284, gen.XM_087284
Figure 1076: DNA324282, NM_002948, gen.NM_002948
Figure 1077: PRO6360
Figure 1078: DNA324283, XM_053323, gen.XM_053323
Figure 1079A-B: DNA324284, NM_001068, gen.NM_001068
Figure 1080: PRO80966
Figure 1081: DNA252367, NM_017801, gen.NM_017801
Figure 1082: PRO48357
Figure 1083: DNA324285, XM_093624, gen.XM_093624
Figure 1084: PRO80967

Figure 1085: DNA324286, XM_046401, gen.XM_046401
Figure 1086: DNA324287, NM_022461, gen.NM_022461
Figure 1087: PRO80969
Figure 1088: DNA324288, XM_113410, gen.XM_113410
Figure 1089: DNA88100, NM_000404, gen.NM_000404
Figure 1090: PRO2172
Figure 1091: DNA324289, XM_091076, gen.XM_091076
Figure 1092: PRO80970
Figure 1093A-B: DNA271187, NM_005109, gen.NM_005109
Figure 1094: PRO59504
Figure 1095: DNA324290, NM_002468, gen.NM_002468
Figure 1096: PRO36735
Figure 1097: DNA269930, NM_001607, gen.NM_001607
Figure 1098: PRO58328
Figure 1099: DNA270401, NM_003149, gen.NM_003149
Figure 1100: PRO58784
Figure 1101: DNA324291, XM_087370, gen.XM_087370
Figure 1102: PRO80971
Figure 1103: DNA324292, XM_098158, gen.XM_098158
Figure 1104: PRO80972
Figure 1105: DNA324293, XM_017364, gen.XM_017364
Figure 1106: DNA324294, XM_087349, gen.XM_087349
Figure 1107: PRO80974
Figure 1108: DNA226547, NM_002295, gen.NM_002295
Figure 1109: PRO37010
Figure 1110: DNA324295, NM_003973, gen.NM_003973
Figure 1111: PRO80975
Figure 1112: DNA324296, XM_030417, gen.XM_030417
Figure 1113: DNA324297, NM_020347, gen.NM_020347
Figure 1114: PRO80977
Figure 1115: DNA324298, XM_087346, gen.XM_087346
Figure 1116: PRO80978
Figure 1117: DNA324299, XM_096198, gen.XM_096198
Figure 1118: PRO80979
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Figure 1120: DNA324301, XM_087588, gen.XM_087588
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Figure 1122A-B: DNA324303, XM_114364, gen.XM_114364
Figure 1123A-B: DNA324304, XM_033294, gen.XM_033294
Figure 1124: PRO80983
Figure 1125: DNA324305, NM_138614, gen.NM_138614
Figure 1126: PRO80984
Figure 1127: DNA324306, XM_002899, gen.XM_002899
Figure 1128: DNA225910, NM_004345, gen.NM_004345
Figure 1129: PRO36373
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Figure 1131: DNA324308, XM_051518, gen.XM_051518
Figure 1132A-D: DNA324309, NM_001407, gen.NM_001407
Figure 1133: PRO50095
Figure 1134: DNA324310, NM_003365, gen.NM_003365
Figure 1135: PRO80988
Figure 1136: DNA324311, XM_003245, gen.XM_003245
Figure 1137: DNA324312, XM_047561, gen.XM_047561
Figure 1138: PRO80990
Figure 1139: DNA324313, XM_116853, gen.XM_116853
Figure 1140A-B: DNA324314, XM_113405, gen.XM_113405
Figure 1141: DNA324315, XM_114323, gen.XM_114323
Figure 1142: PRO80993
Figure 1143: DNA324316, XM_002828, gen.XM_002828
Figure 1144: PRO80994
Figure 1145: DNA150976, NM_022171, gen.NM_022171
Figure 1146: PRO12565
Figure 1147: DNA324317, XM_041507, gen.XM_041507
Figure 1148: PRO71103
Figure 1149: DNA103505, NM_004636, gen.NM_004636
Figure 1150: PRO4832
Figure 1151: DNA324318, NM_006764, gen.NM_006764
Figure 1152: PRO80995
Figure 1153: DNA150562, NM_007275, gen.NM_007275
Figure 1154: PRO12779

Figure 1155: DNA254582, NM_004635, gen.NM_004635
Figure 1156: PRO49685
Figure 1157: DNA324319, NM_052859, gen.NM_052859
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Figure 1162: DNA324322, XM_003213, gen.XM_003213
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Figure 1164: PRO80999
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Figure 1166: PRO37770
Figure 1167: DNA324324, NM_000688, gen.NM_000688
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Figure 1169: DNA324325, XM_067715, gen.XM_067715
Figure 1170: DNA324326, NM_000992, gen.NM_000992
Figure 1171: PRO62153
Figure 1172: DNA324327, NM_000666, gen.NM_000666
Figure 1173: PRO81002
Figure 1174: DNA324328, NM_032750, gen.NM_032750
Figure 1175: PRO81003
Figure 1176: DNA324329, NM_033008, gen.NM_033008
Figure 1177: PRO81004
Figure 1178: DNA324330, NM_033010, gen.NM_033010
Figure 1179: PRO81005
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Figure 1181: PRO81006
Figure 1182: DNA273919, NM_004704, gen.NM_004704
Figure 1183: PRO61870
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Figure 1185: PRO81007
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Figure 1188: DNA0, NM_002854, gen.NM_002854
Figure 1189: PRO
Figure 1190: DNA324335, XM_096195, gen.XM_096195

Figure 1191: PRO81010
Figure 1192: DNA324336, XM_166015, gen.XM_166015
Figure 1193: DNA324337, XM_113395, gen.XM_113395
Figure 1194: PRO81012
Figure 1195: DNA269730, NM_014814, gen.NM_014814
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Figure 1197: DNA324338, XM_036938, gen.XM_036938
Figure 1198: DNA324339, XM_029369, gen.XM_029369
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Figure 1202: DNA324342, XM_113409, gen.XM_113409
Figure 1203: DNA324343, XM_087268, gen.XM_087268
Figure 1204: DNA324344, XM_116071, gen.XM_116071
Figure 1205: DNA324345, XM_116072, gen.XM_116072
Figure 1206: DNA324346, NM_000986, gen.NM_000986
Figure 1207: PRO10602
Figure 1208: DNA324347, XM_015462, gen.XM_015462
Figure 1209: DNA324348, XM_167366, gen.XM_167366
Figure 1210: PRO81022
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Figure 1213: DNA324350, XM_039952, gen.XM_039952
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Figure 1219: PRO81026
Figure 1220: DNA324354, XM_027161, gen.XM_027161
Figure 1221A-B: DNA324355, XM_032269, gen.XM_032269
Figure 1222: PRO81028
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Figure 1224: PRO2837

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Figure 1227: DNA324357, XM_098173, gen.XM_098173
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Figure 1229: DNA324358, XM_042618, gen.XM_042618
Figure 1230: PRO81031
Figure 1231: DNA324359, XM_084129, gen.XM_084129
Figure 1232: DNA324360, XM_098154, gen.XM_098154
Figure 1233: PRO81033
Figure 1234: DNA324361, XM_050552, gen.XM_050552
Figure 1235: DNA324362, NM_032343, gen.NM_032343
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Figure 1237: DNA324363, XM_051264, gen.XM_051264
Figure 1238A-B: DNA324364, NM_013336, gen.NM_013336
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Figure 1244: DNA324368, XM_113397, gen.XM_113397
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Figure 1246: DNA324370, NM_004637, gen.NM_004637
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Figure 1260: DNA324378, NM_000532, gen.NM_000532
Figure 1261: PRO81047
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Figure 1263: DNA324380, XM_084123, gen.XM_084123
Figure 1264: DNA324381, XM_018149, gen.XM_018149
Figure 1265: DNA324382, XM_087342, gen.XM_087342
Figure 1266: DNA324383, XM_059516, gen.XM_059516
Figure 1267: DNA324384, XM_087341, gen.XM_087341
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Figure 1269: PRO81053
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Figure 1278: DNA324390, XM_058267, gen.XM_058267
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Figure 1292A-B: DNA324399, XM_039796,

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 Figure 1294: DNA324400, XM_016334, gen.XM_016334
 Figure 1295: DNA324401, XM_116058, gen.XM_116058
 Figure 1296: DNA324402, XM_113408, gen.XM_113408
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Figure 1391: PRO81115
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Figure 1403: PRO81120
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Figure 1457A-B: DNA324494, NM_014933, gen.NM_014933
Figure 1458: PRO81150
Figure 1459: DNA290585, NM_000582, gen.NM_000582
Figure 1460: PRO70536
Figure 1461: DNA324495, XM_055551, gen.XM_055551
Figure 1462: PRO81151
Figure 1463: DNA324496, XM_087498, gen.XM_087498
Figure 1464: DNA324497, XM_096203, gen.XM_096203
Figure 1465: DNA324498, XM_084158, gen.XM_084158
Figure 1466: DNA324499, XM_034710, gen.XM_034710
Figure 1467: PRO81156
Figure 1468: DNA324500, XM_034713, gen.XM_034713
Figure 1469: DNA324501, XM_059633, gen.XM_059633
Figure 1470: DNA324502, XM_114426, gen.XM_114426
Figure 1471: DNA324503, XM_056957, gen.XM_056957
Figure 1472: DNA324504, XM_088472, gen.XM_088472
Figure 1473: DNA324505, XM_114424, gen.XM_114424
Figure 1474A-B: DNA324506, XM_042301, gen.XM_042301
Figure 1475: PRO81163
Figure 1476: DNA324507, XM_017925, gen.XM_017925
Figure 1477: DNA324508, XM_052336, gen.XM_052336
Figure 1478: DNA324509, NM_002106, gen.NM_002106
Figure 1479: PRO10297
Figure 1480: DNA324510, XM_085068, gen.XM_085068
Figure 1481: PRO81166
Figure 1482: DNA324511, XM_165473, gen.XM_165473
Figure 1483: DNA324512, XM_087514, gen.XM_087514
Figure 1484: DNA324513, XM_116247, gen.XM_116247
Figure 1485: DNA324514, NM_002358, gen.NM_002358
Figure 1486: PRO81169
Figure 1487: DNA324515, XM_050200, gen.XM_050200
Figure 1488: PRO81170
Figure 1489: DNA225584, NM_001154, gen.NM_001154
Figure 1490: PRO36047
Figure 1491: DNA324516, NM_024900, gen.NM_024900
Figure 1492: PRO81171
Figure 1493: DNA324517, XM_040752, gen.XM_040752
Figure 1494: DNA324518, NM_002413, gen.NM_002413
Figure 1495: PRO60956
Figure 1496: DNA324519, XM_114401, gen.XM_114401

Figure 1497: DNA324520, XM_068164, gen.XM_068164
Figure 1498: PRO81174
Figure 1499: DNA324521, XM_060067, gen.XM_060067
Figure 1500: DNA324522, XM_003555, gen.XM_003555
Figure 1501: PRO81176
Figure 1502: DNA324523, XM_034321, gen.XM_034321
Figure 1503: PRO81177
Figure 1504: DNA324524, NM_006439, gen.NM_006439
Figure 1505: PRO81178
Figure 1506: DNA324525, NM_001006, gen.NM_001006
Figure 1507: PRO81179
Figure 1508: DNA227575, NM_005141, gen.NM_005141
Figure 1509: PRO38038
Figure 1510: DNA324526, XM_114368, gen.XM_114368
Figure 1511A-B: DNA225920, NM_000508, gen.NM_000508
Figure 1512: PRO36383
Figure 1513: DNA324527, NM_021871, gen.NM_021871
Figure 1514: PRO81181
Figure 1515: DNA225921, NM_000509, gen.NM_000509
Figure 1516: PRO36384
Figure 1517: DNA324528, NM_021870, gen.NM_021870
Figure 1518: PRO81182
Figure 1519: DNA324529, XM_059623, gen.XM_059623
Figure 1520: DNA324530, XM_106246, gen.XM_106246
Figure 1521: PRO81184
Figure 1522: DNA324531, NM_002129, gen.NM_002129
Figure 1523: PRO81185
Figure 1524: DNA324532, XM_040321, gen.XM_040321
Figure 1525: DNA324533, XM_015563, gen.XM_015563
Figure 1526: DNA324534, NM_024748, gen.NM_024748
Figure 1527: PRO81188
Figure 1528: DNA324535, XM_165470, gen.XM_165470
Figure 1529: PRO81189
Figure 1530A-E: DNA324536, XM_003477, gen.XM_003477
Figure 1531: DNA324537, XM_165465, gen.XM_165465
Figure 1532: DNA324538, XM_116204, gen.XM_116204
Figure 1533: DNA324539, XM_116205, gen.XM_116205
Figure 1534: DNA324540, XM_098405, gen.XM_098405
Figure 1535: DNA324541, XM_052313, gen.XM_052313
Figure 1536: PRO81195
Figure 1537: DNA324542, XM_087659, gen.XM_087659
Figure 1538: PRO81196
Figure 1539: DNA324543, XM_029096, gen.XM_029096
Figure 1540: DNA324544, XM_003825, gen.XM_003825
Figure 1541: DNA324545, XM_057994, gen.XM_057994
Figure 1542: PRO81199
Figure 1543: DNA324546, XM_087686, gen.XM_087686
Figure 1544: DNA324547, XM_017641, gen.XM_017641
Figure 1545: DNA324548, NM_030782, gen.NM_030782
Figure 1546: PRO81202
Figure 1547: DNA324549, XM_084168, gen.XM_084168
Figure 1548: DNA324550, XM_057492, gen.XM_057492
Figure 1549: DNA324551, XM_087597, gen.XM_087597
Figure 1550: DNA324552, XM_087601, gen.XM_087601
Figure 1551: DNA324554, XM_087599, gen.XM_087599
Figure 1552: DNA324555, XM_114435, gen.XM_114435
Figure 1553: DNA324556, XM_087600, gen.XM_087600
Figure 1554: DNA324557, XM_016170, gen.XM_016170
Figure 1555: DNA324558, XM_114434, gen.XM_114434
Figure 1556: DNA324559, XM_113452, gen.XM_113452
Figure 1557: DNA324560, XM_071580, gen.XM_071580
Figure 1558: PRO81213
Figure 1559: DNA324561, XM_087713, gen.XM_087713
Figure 1560: PRO81214
Figure 1561: DNA324562, XM_094440, gen.XM_094440
Figure 1562: DNA324563, XM_106739, gen.XM_106739

Figure 1563: PRO81216
Figure 1564: DNA324564, XM_087614, gen.XM_087614
Figure 1565: DNA324565, XM_004009, gen.XM_004009
Figure 1566: PRO81219
Figure 1567: DNA324566, XM_114437, gen.XM_114437
Figure 1568: DNA324567, XM_043771, gen.XM_043771
Figure 1569: PRO81221
Figure 1570: DNA324568, NM_000997, gen.NM_000997
Figure 1571: PRO11077
Figure 1572: DNA324569, XM_003869, gen.XM_003869
Figure 1573: DNA227173, NM_001465, gen.NM_001465
Figure 1574: PRO37636
Figure 1575: DNA324570, NM_018034, gen.NM_018034
Figure 1576: PRO81223
Figure 1577: DNA324571, NM_032637, gen.NM_032637
Figure 1578: PRO81224
Figure 1579: DNA324572, NM_005983, gen.NM_005983
Figure 1580: PRO81225
Figure 1581A-B: DNA324573, XM_003896, gen.XM_003896
Figure 1582: DNA287282, NM_002130, gen.NM_002130
Figure 1583: PRO69554
Figure 1584: DNA324574, XM_114442, gen.XM_114442
Figure 1585: PRO81227
Figure 1586: DNA324575, XM_114439, gen.XM_114439
Figure 1587: DNA324576, XM_114440, gen.XM_114440
Figure 1588A-B: DNA324577, XM_032902, gen.XM_032902
Figure 1589: PRO81230
Figure 1590: DNA324578, XM_032895, gen.XM_032895
Figure 1591: DNA324579, XM_084179, gen.XM_084179
Figure 1592: DNA324580, XM_041712, gen.XM_041712
Figure 1593: DNA324581, XM_116439, gen.XM_116439
Figure 1594: PRO81234
Figure 1595: DNA324582, XM_087611, gen.XM_087611
Figure 1596: DNA324583, XM_059653, gen.XM_059653

Figure 1597: DNA324584, XM_087610, gen.XM_087610
Figure 1598: DNA288259, NM_031966, gen.NM_031966
Figure 1599: PRO4676
Figure 1600: DNA324585, XM_042025, gen.XM_042025
Figure 1601: PRO81238
Figure 1602: DNA324586, NM_005713, gen.NM_005713
Figure 1603: PRO81239
Figure 1604: DNA324587, XM_059709, gen.XM_059709
Figure 1605: PRO81240
Figure 1606: DNA324588, XM_116447, gen.XM_116447
Figure 1607: PRO81241
Figure 1608: DNA324589, XM_037260, gen.XM_037260
Figure 1609: DNA324590, XM_098351, gen.XM_098351
Figure 1610: DNA324591, XM_098354, gen.XM_098354
Figure 1611: DNA324592, XM_098352, gen.XM_098352
Figure 1612: DNA324593, XM_166037, gen.XM_166037
Figure 1613: PRO81246
Figure 1614: DNA324594, XM_041694, gen.XM_041694
Figure 1615: DNA324595, XM_165488, gen.XM_165488
Figure 1616: PRO81248
Figure 1617: DNA324596, XM_059669, gen.XM_059669
Figure 1618: PRO81249
Figure 1619: DNA324597, XM_027964, gen.XM_027964
Figure 1620: PRO81250
Figure 1621: DNA324598, XM_088020, gen.XM_088020
Figure 1622: DNA324599, XM_117387, gen.XM_117387
Figure 1623: DNA324600, XM_114469, gen.XM_114469
Figure 1624: DNA324601, NM_001207, gen.NM_001207
Figure 1625: PRO22771
Figure 1626A-B: DNA324602, XM_032553, gen.XM_032553
Figure 1627: DNA254147, NM_000521, gen.NM_000521
Figure 1628: PRO49262
Figure 1629: DNA324603, NM_031482, gen.NM_031482
Figure 1630: PRO81254

Figure 1631: DNA324604, XM_087790, gen.XM_087790
Figure 1632: DNA324605, NM_001025, gen.NM_001025
Figure 1633: PRO10685
Figure 1634: DNA324606, XM_098362, gen.XM_098362
Figure 1635: PRO81256
Figure 1636: DNA324607, NM_003401, gen.NM_003401
Figure 1637: PRO70327
Figure 1638: DNA290231, NM_022550, gen.NM_022550
Figure 1639: PRO70327
Figure 1640: DNA324608, XM_017857, gen.XM_017857
Figure 1641: DNA324609, XM_117398, gen.XM_117398
Figure 1642A-B: DNA257253, NM_032280, gen.NM_032280
Figure 1643: PRO51851
Figure 1644: DNA324610, XM_003771, gen.XM_003771
Figure 1645: PRO81259
Figure 1646A-B: DNA269816, NM_002397, gen.NM_002397
Figure 1647: PRO58219
Figure 1648: DNA324611, XM_116427, gen.XM_116427
Figure 1649: PRO81260
Figure 1650: DNA324612, NM_004772, gen.NM_004772
Figure 1651: PRO81261
Figure 1652: DNA324613, XM_016674, gen.XM_016674
Figure 1653: PRO81262
Figure 1654: DNA324614, XM_113463, gen.XM_113463
Figure 1655: DNA324615, XM_034744, gen.XM_034744
Figure 1656: DNA324616, XM_087745, gen.XM_087745
Figure 1657: PRO81264
Figure 1658: DNA324617, XM_018473, gen.XM_018473
Figure 1659: PRO81265
Figure 1660: DNA324618, XM_087635, gen.XM_087635
Figure 1661: PRO81266
Figure 1662: DNA324619, XM_087637, gen.XM_087637
Figure 1663: DNA324620, XM_166027, gen.XM_166027
Figure 1664: DNA324621, NM_014035, gen.NM_014035
Figure 1665: PRO1285
Figure 1666: DNA324622, XM_003830, gen.XM_003830
Figure 1667: PRO81269
Figure 1668: DNA324623, XM_037002, gen.XM_037002
Figure 1669: DNA324624, XM_166026, gen.XM_166026
Figure 1670: DNA324625, XM_041059, gen.XM_041059
Figure 1671: DNA83020, NM_000358, gen.NM_000358
Figure 1672: PRO2561
Figure 1673: DNA324626, NM_003687, gen.NM_003687
Figure 1674: PRO81272
Figure 1675: DNA324627, XM_034862, gen.XM_034862
Figure 1676: PRO34544
Figure 1677: DNA103380, NM_003374, gen.NM_003374
Figure 1678: PRO4710
Figure 1679: DNA324628, XM_017474, gen.XM_017474
Figure 1680: PRO63082
Figure 1681A-B: DNA324629, NM_014829, gen.NM_014829
Figure 1682: PRO81273
Figure 1683A-B: DNA324630, XM_114482, gen.XM_114482
Figure 1684: PRO81274
Figure 1685: DNA324631, NM_004893, gen.NM_004893
Figure 1686: PRO81275
Figure 1687: DNA269809, NM_006805, gen.NM_006805
Figure 1688: PRO58213
Figure 1689: DNA226872, NM_001964, gen.NM_001964
Figure 1690: PRO37335
Figure 1691: DNA324632, XM_116307, gen.XM_116307
Figure 1692: PRO81276
Figure 1693: DNA324633, NM_004134, gen.NM_004134
Figure 1694: PRO81277
Figure 1695: DNA324634, XM_038221, gen.XM_038221
Figure 1696: PRO81278
Figure 1697: DNA271931, NM_005754, gen.NM_005754
Figure 1698: PRO60207
Figure 1699: DNA324635, XM_003841, gen.XM_003841
Figure 1700: DNA324636, XM_032759, gen.XM_032759
Figure 1701: DNA324637, XM_017591,

gen.XM_017591
Figure 1702: DNA324638, NM_006058,
gen.NM_006058
Figure 1703: PRO81280
Figure 1704: DNA324639, NM_002084,
gen.NM_002084
Figure 1705: PRO81281
Figure 1706: DNA324640, NM_018047,
gen.NM_018047
Figure 1707: PRO81282
Figure 1708: DNA324641, NM_005617,
gen.NM_005617
Figure 1709: PRO10849
Figure 1710: DNA324642, XM_003937,
gen.XM_003937
Figure 1711: DNA324643, XM_087621,
gen.XM_087621
Figure 1712A-B: DNA324644, XM_003789,
gen.XM_003789
Figure 1713: DNA324645, XM_087652,
gen.XM_087652
Figure 1714: DNA324646, XM_068853,
gen.XM_068853
Figure 1715: PRO81286
Figure 1716: DNA324647, XM_116465,
gen.XM_116465
Figure 1717: PRO81287
Figure 1718: DNA302020, NM_005573,
gen.NM_005573
Figure 1719: PRO70993
Figure 1720: DNA324648, XM_113467,
gen.XM_113467
Figure 1721: DNA271626, NM_014773,
gen.NM_014773
Figure 1722: PRO59913
Figure 1723A-B: DNA324649, XM_056315,
gen.XM_056315
Figure 1724: DNA324650, NM_024668,
gen.NM_024668
Figure 1725: PRO81289
Figure 1726: DNA324651, NM_080670,
gen.NM_080670
Figure 1727: PRO81290
Figure 1728A-B: DNA324652, NM_002588,
gen.NM_002588
Figure 1729: PRO81291
Figure 1730A-B: DNA324653, NM_003735,
gen.NM_003735
Figure 1731: PRO81292
Figure 1732A-B: DNA150679, NM_003736,
gen.NM_003736
Figure 1733: PRO12416
Figure 1734A-B: DNA324654, NM_018912,
gen.NM_018912
Figure 1735: PRO36058
Figure 1736A-B: DNA324655, NM_018913,
gen.NM_018913
Figure 1737: PRO81293
Figure 1738A-B: DNA324656, NM_018914,
gen.NM_018914
Figure 1739: PRO81294
Figure 1740A-B: DNA324657, NM_018915,
gen.NM_018915
Figure 1741: PRO36020
Figure 1742A-B: DNA324658, NM_018916,
gen.NM_018916
Figure 1743: PRO81295
Figure 1744A-B: DNA324659, NM_018917,
gen.NM_018917
Figure 1745: PRO81296
Figure 1746A-B: DNA324660, NM_018918,
gen.NM_018918
Figure 1747: PRO81297
Figure 1748A-B: DNA324661, NM_018919,
gen.NM_018919
Figure 1749: PRO81298
Figure 1750A-B: DNA324662, NM_018920,
gen.NM_018920
Figure 1751: PRO81299
Figure 1752A-B: DNA324663, NM_018921,
gen.NM_018921
Figure 1753: PRO81300
Figure 1754A-B: DNA324664, NM_018922,
gen.NM_018922
Figure 1755: PRO81301
Figure 1756A-B: DNA324665, NM_018923,
gen.NM_018923
Figure 1757: PRO81302
Figure 1758A-B: DNA324666, NM_018924,
gen.NM_018924
Figure 1759: PRO81303
Figure 1760A-B: DNA324667, NM_018925,
gen.NM_018925
Figure 1761: PRO81304
Figure 1762A-B: DNA324668, NM_018926,
gen.NM_018926
Figure 1763: PRO81305
Figure 1764A-B: DNA324669, NM_018927,
gen.NM_018927
Figure 1765: PRO37091
Figure 1766A-B: DNA324670, NM_018928,
gen.NM_018928
Figure 1767: PRO81306
Figure 1768A-B: DNA324671, NM_018929,
gen.NM_018929
Figure 1769: PRO81307
Figure 1770A-B: DNA324672, NM_032088,
gen.NM_032088
Figure 1771: PRO81308
Figure 1772A-B: DNA324673, NM_032092,
gen.NM_032092
Figure 1773: PRO81309

Figure 1774: DNA324674, NM_032403, gen.NM_032403
Figure 1775: PRO81310
Figure 1776: DNA324675, NM_032402, gen.NM_032402
Figure 1777: PRO81311
Figure 1778: DNA324676, XM_098387, gen.XM_098387
Figure 1779: DNA324677, NM_002109, gen.NM_002109
Figure 1780: PRO4908
Figure 1781: DNA324678, XM_084180, gen.XM_084180
Figure 1782: PRO81313
Figure 1783: DNA324679, XM_039975, gen.XM_039975
Figure 1784: PRO81314
Figure 1785: DNA324680, NM_033551, gen.NM_033551
Figure 1786: PRO81315
Figure 1787: DNA324681, NM_004821, gen.NM_004821
Figure 1788: PRO81316
Figure 1789: DNA324682, XM_068395, gen.XM_068395
Figure 1790: PRO81317
Figure 1791: DNA226418, NM_004060, gen.NM_004060
Figure 1792: PRO36881
Figure 1793A-B: DNA324683, XM_056963, gen.XM_056963
Figure 1794: PRO81318
Figure 1795: DNA324684, NM_004219, gen.NM_004219
Figure 1796: PRO81319
Figure 1797: DNA324685, XM_094243, gen.XM_094243
Figure 1798A-B: DNA324686, XM_047964, gen.XM_047964
Figure 1799: DNA324687, XM_016345, gen.XM_016345
Figure 1800: DNA324688, NM_002887, gen.NM_002887
Figure 1801: PRO81323
Figure 1802: DNA324689, XM_166029, gen.XM_166029
Figure 1803: DNA324690, NM_002520, gen.NM_002520
Figure 1804: PRO58993
Figure 1805: DNA324691, XM_043340, gen.XM_043340
Figure 1806: PRO81325
Figure 1807: DNA324692, XM_116340, gen.XM_116340
Figure 1808A-B: DNA324693, XM_043388, gen.XM_043388
Figure 1809: PRO81327
Figure 1810: DNA324694, XM_116856, gen.XM_116856
Figure 1811: DNA324695, XM_003716, gen.XM_003716
Figure 1812: DNA227320, NM_003714, gen.NM_003714
Figure 1813: PRO37783
Figure 1814: DNA324696, NM_032361, gen.NM_032361
Figure 1815: PRO81330
Figure 1816: DNA324697, XM_087773, gen.XM_087773
Figure 1817: DNA324698, XM_114457, gen.XM_114457
Figure 1818: DNA324699, XM_165483, gen.XM_165483
Figure 1819: DNA324700, XM_114453, gen.XM_114453
Figure 1820: DNA324701, XM_165484, gen.XM_165484
Figure 1821: DNA324702, XM_030771, gen.XM_030771
Figure 1822: PRO19615
Figure 1823: DNA324703, XM_030777, gen.XM_030777
Figure 1824: DNA324704, XM_030782, gen.XM_030782
Figure 1825: PRO81336
Figure 1826: DNA324705, NM_030567, gen.NM_030567
Figure 1827: PRO81337
Figure 1828: DNA225909, NM_000505, gen.NM_000505
Figure 1829: PRO36372
Figure 1830: DNA274206, NM_006816, gen.NM_006816
Figure 1831: PRO62135
Figure 1832: DNA324706, NM_031300, gen.NM_031300
Figure 1833: PRO81338
Figure 1834: DNA324707, NM_013237, gen.NM_013237
Figure 1835: PRO81339
Figure 1836: DNA324708, NM_002011, gen.NM_002011
Figure 1837: PRO81340
Figure 1838: DNA324709, NM_022963, gen.NM_022963
Figure 1839: PRO81341
Figure 1840: DNA324710, XM_038946, gen.XM_038946
Figure 1841: DNA324711, XM_113454, gen.XM_113454
Figure 1842: DNA324712, XM_166028, gen.XM_166028

Figure 1843: DNA324713, NM_015043, gen.NM_015043
Figure 1844: PRO81345
Figure 1845: DNA324714, XM_113468, gen.XM_113468
Figure 1846: DNA324715, NM_014275, gen.NM_014275
Figure 1847: PRO1927
Figure 1848: DNA324716, NM_054013, gen.NM_054013
Figure 1849: PRO81347
Figure 1850: DNA270675, NM_005520, gen.NM_005520
Figure 1851: PRO59040
Figure 1852: DNA324717, NM_006098, gen.NM_006098
Figure 1853: PRO25849
Figure 1854: DNA269593, NM_005110, gen.NM_005110
Figure 1855: PRO58006
Figure 1856: DNA324718, XM_116365, gen.XM_116365
Figure 1857: DNA324719, XM_116511, gen.XM_116511
Figure 1858: DNA324720, XM_087823, gen.XM_087823
Figure 1859A-C: DNA324721, XM_053955, gen.XM_053955
Figure 1860: DNA324722, XM_113476, gen.XM_113476
Figure 1861: DNA324723, XM_116514, gen.XM_116514
Figure 1862: DNA324724, XM_094741, gen.XM_094741
Figure 1863: DNA324725, NM_025168, gen.NM_025168
Figure 1864: PRO81354
Figure 1865A-B: DNA324726, XM_165740, gen.XM_165740
Figure 1866: DNA272171, NM_002388, gen.NM_002388
Figure 1867: PRO60438
Figure 1868: DNA324727, XM_167169, gen.XM_167169
Figure 1869: PRO81355
Figure 1870: DNA324728, NM_014452, gen.NM_014452
Figure 1871: PRO868
Figure 1872: DNA324729, XM_166349, gen.XM_166349
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Figure 1874: DNA304680, NM_007355, gen.NM_007355
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Figure 1876: DNA324730, XM_165772, gen.XM_165772
Figure 1877: DNA324731, XM_168123, gen.XM_168123
Figure 1878: DNA324732, XM_166457, gen.XM_166457
Figure 1879: DNA324733, XM_166469, gen.XM_166469
Figure 1880: DNA324734, NM_018135, gen.NM_018135
Figure 1881: PRO81359
Figure 1882A-B: DNA324735, XM_166340, gen.XM_166340
Figure 1883: DNA324736, XM_087960, gen.XM_087960
Figure 1884: DNA324737, XM_166362, gen.XM_166362
Figure 1885: PRO81362
Figure 1886: DNA227204, NM_015388, gen.NM_015388
Figure 1887: PRO37667
Figure 1888: DNA324738, XM_166425, gen.XM_166425
Figure 1889: PRO81363
Figure 1890: DNA324739, NM_057161, gen.NM_057161
Figure 1891: PRO81364
Figure 1892: DNA270613, NM_006245, gen.NM_006245
Figure 1893: PRO58984
Figure 1894: DNA324740, NM_006586, gen.NM_006586
Figure 1895: PRO81365
Figure 1896: DNA324741, XM_166402, gen.XM_166402
Figure 1897: PRO81366
Figure 1898: DNA324742, NM_001760, gen.NM_001760
Figure 1899: PRO81367
Figure 1900: DNA287246, NM_004053, gen.NM_004053
Figure 1901: PRO69521
Figure 1902: DNA324743, NM_017601, gen.NM_017601
Figure 1903: PRO81368
Figure 1904: DNA275630, NM_006708, gen.NM_006708
Figure 1905: PRO63253
Figure 1906: DNA324744, NM_014341, gen.NM_014341
Figure 1907: PRO81369
Figure 1908: DNA304460, NM_016059, gen.NM_016059
Figure 1909: PRO4984
Figure 1910: DNA324745, XM_166412, gen.XM_166412
Figure 1911: PRO81370
Figure 1912: DNA304716, NM_078467,

gen.NM_078467
 Figure 1913: PRO71142
 Figure 1914: DNA324746, XM_166417,
 gen.XM_166417
 Figure 1915: PRO81371
 Figure 1916A-B: DNA324747, NM_003137,
 gen.NM_003137
 Figure 1917: PRO81372
 Figure 1918A-B: DNA324748, NM_004117,
 gen.NM_004117
 Figure 1919: PRO36841
 Figure 1920: DNA324749, XM_166419,
 gen.XM_166419
 Figure 1921: DNA324750, XM_165794,
 gen.XM_165794
 Figure 1922: DNA324751, NM_007104,
 gen.NM_007104
 Figure 1923: PRO10360
 Figure 1924: DNA324752, NM_024294,
 gen.NM_024294
 Figure 1925: PRO81375
 Figure 1926: DNA324753, NM_022758,
 gen.NM_022758
 Figure 1927: PRO50582
 Figure 1928: DNA324754, XM_168070,
 gen.XM_168070
 Figure 1929: DNA324755, NM_012391,
 gen.NM_012391
 Figure 1930: PRO81377
 Figure 1931: DNA324756, XM_166459,
 gen.XM_166459
 Figure 1932: DNA324757, XM_166333,
 gen.XM_166333
 Figure 1933: PRO81379
 Figure 1934: DNA324758, XM_058039,
 gen.XM_058039
 Figure 1935: PRO81380
 Figure 1936: DNA324759, XM_087990,
 gen.XM_087990
 Figure 1937: DNA324760, XM_165743,
 gen.XM_165743
 Figure 1938: DNA324761, XM_166360,
 gen.XM_166360
 Figure 1939: DNA324763, XM_059801,
 gen.XM_059801
 Figure 1940: DNA324764, XM_166363,
 gen.XM_166363
 Figure 1941: DNA324765, XM_016857,
 gen.XM_016857
 Figure 1942: DNA227442, NM_001350,
 gen.NM_001350
 Figure 1943: PRO37905
 Figure 1944: DNA324766, NM_005452,
 gen.NM_005452
 Figure 1945: PRO81387
 Figure 1946: DNA304661, NM_022551,
 gen.NM_022551
 Figure 1947: PRO71088
 Figure 1948: DNA324767, XM_165747,
 gen.XM_165747
 Figure 1949: DNA324768, XM_165698,
 gen.XM_165698
 Figure 1950: PRO4884
 Figure 1951A-B: DNA324769, XM_165770,
 gen.XM_165770
 Figure 1952: DNA287227, NM_004159,
 gen.NM_004159
 Figure 1953: PRO69506
 Figure 1954: DNA324770, XM_165717,
 gen.XM_165717
 Figure 1955: DNA324771, XM_166480,
 gen.XM_166480
 Figure 1956: DNA324772, XM_165801,
 gen.XM_165801
 Figure 1957A-B: DNA324773, NM_000592,
 gen.NM_000592
 Figure 1958: PRO36316
 Figure 1959: DNA324774, NM_001710,
 gen.NM_001710
 Figure 1960: PRO36305
 Figure 1961: DNA227607, NM_005346,
 gen.NM_005346
 Figure 1962: PRO38070
 Figure 1963: DNA304668, NM_005345,
 gen.NM_005345
 Figure 1964: PRO71095
 Figure 1965: DNA324775, NM_021177,
 gen.NM_021177
 Figure 1966: PRO81394
 Figure 1967A-B: DNA272263, NM_006295,
 gen.NM_006295
 Figure 1968: PRO70138
 Figure 1969: DNA287319, NM_001288,
 gen.NM_001288
 Figure 1970: PRO69584
 Figure 1971: DNA324776, NM_001320,
 gen.NM_001320
 Figure 1972: PRO63052
 Figure 1973A-B: DNA324777, NM_004639,
 gen.NM_004639
 Figure 1974: PRO81395
 Figure 1975A-B: DNA324778, NM_080703,
 gen.NM_080703
 Figure 1976: PRO81396
 Figure 1977A-B: DNA324779, NM_080702,
 gen.NM_080702
 Figure 1978: PRO81397
 Figure 1979A-B: DNA324780, NM_004638,
 gen.NM_004638
 Figure 1980: PRO81398
 Figure 1981A-B: DNA324781, NM_080686,
 gen.NM_080686

Figure 1982: PRO81399
Figure 1983: DNA324782, XM_165771, gen.XM_165771
Figure 1984: DNA324783, NM_080598, gen.NM_080598
Figure 1985: PRO71125
Figure 1986: DNA304699, NM_004640, gen.NM_004640
Figure 1987: PRO71125
Figure 1988: DNA324784, XM_165765, gen.XM_165765
Figure 1989: PRO81400
Figure 1990: DNA324785, XM_087945, gen.XM_087945
Figure 1991: PRO81401
Figure 1992: DNA324786, XM_166381, gen.XM_166381
Figure 1993: PRO81402
Figure 1994: DNA324787, XM_168104, gen.XM_168104
Figure 1995: DNA324788, XM_166401, gen.XM_166401
Figure 1996: PRO81404
Figure 1997: DNA271040, NM_001517, gen.NM_001517
Figure 1998: PRO59365
Figure 1999A-B: DNA324789, XM_165738, gen.XM_165738
Figure 2000: DNA324790, XM_087939, gen.XM_087939
Figure 2001: PRO81406
Figure 2002: DNA324791, XM_166353, gen.XM_166353
Figure 2003: PRO1112
Figure 2004A-B: DNA324792, XM_166376, gen.XM_166376
Figure 2005: PRO81407
Figure 2006A-B: DNA324793, XM_165799, gen.XM_165799
Figure 2007: DNA290264, NM_025263, gen.NM_025263
Figure 2008: PRO70393
Figure 2009: DNA324794, XM_166361, gen.XM_166361
Figure 2010: PRO81409
Figure 2011: DNA324795, XM_165764, gen.XM_165764
Figure 2012: PRO81410
Figure 2013: DNA324796, XM_165758, gen.XM_165758
Figure 2014: PRO81411
Figure 2015: DNA324797, XM_166406, gen.XM_166406
Figure 2016: DNA324798, XM_165809, gen.XM_165809
Figure 2017: DNA324799, NM_018950, gen.NM_018950
Figure 2018: PRO81414
Figure 2019: DNA324800, XM_166392, gen.XM_166392
Figure 2020: PRO81415
Figure 2021: DNA324801, XM_166336, gen.XM_166336
Figure 2022: PRO81416
Figure 2023: DNA324802, XM_167128, gen.XM_167128
Figure 2024: PRO23797
Figure 2025: DNA324803, XM_167161, gen.XM_167161
Figure 2026: PRO81417
Figure 2027: DNA324804, NM_013375, gen.NM_013375
Figure 2028: PRO81418
Figure 2029: DNA324805, NM_007047, gen.NM_007047
Figure 2030: PRO81419
Figure 2031: DNA324806, XM_167179, gen.XM_167179
Figure 2032: DNA290785, NM_003107, gen.NM_003107
Figure 2033: PRO70544
Figure 2034: DNA150772, NM_003472, gen.NM_003472
Figure 2035: PRO12797
Figure 2036A-B: DNA324807, XM_165728, gen.XM_165728
Figure 2037: DNA324808, XM_165749, gen.XM_165749
Figure 2038: PRO81421
Figure 2039A-B: DNA324809, NM_004973, gen.NM_004973
Figure 2040: PRO81422
Figure 2041: DNA324810, XM_167196, gen.XM_167196
Figure 2042: DNA324811, XM_166446, gen.XM_166446
Figure 2043: PRO81424
Figure 2044A-C: DNA324812, XM_165777, gen.XM_165777
Figure 2045: DNA324813, XM_037875, gen.XM_037875
Figure 2046: PRO81426
Figure 2047: DNA324814, XM_167225, gen.XM_167225
Figure 2048: PRO81427
Figure 2049: DNA324815, XM_166357, gen.XM_166357
Figure 2050: DNA324816, NM_001069, gen.NM_001069
Figure 2051: PRO81429
Figure 2052: DNA324817, NM_001500, gen.NM_001500

Figure 2053: PRO81430
Figure 2054A-B: DNA324818, XM_166042, gen.XM_166042
Figure 2055: PRO51389
Figure 2056: DNA324819, XM_052721, gen.XM_052721
Figure 2057: DNA324820, XM_165499, gen.XM_165499
Figure 2058: DNA324821, XM_114497, gen.XM_114497
Figure 2059: DNA324822, XM_011117, gen.XM_011117
Figure 2060: DNA324823, XM_094855, gen.XM_094855
Figure 2061: PRO81435
Figure 2062: DNA324824, XM_059776, gen.XM_059776
Figure 2063: PRO81436
Figure 2064: DNA324825, XM_055641, gen.XM_055641
Figure 2065: DNA324826, XM_004151, gen.XM_004151
Figure 2066: DNA324827, NM_133645, gen.NM_133645
Figure 2067: PRO81439
Figure 2068: DNA324828, XM_097453, gen.XM_097453
Figure 2069: DNA324829, XM_029228, gen.XM_029228
Figure 2070: DNA103471, NM_006670, gen.NM_006670
Figure 2071: PRO4798
Figure 2072: DNA324830, XM_068963, gen.XM_068963
Figure 2073: PRO81441
Figure 2074: DNA324831, XM_040623, gen.XM_040623
Figure 2075: DNA324832, NM_020320, gen.NM_020320
Figure 2076: PRO81443
Figure 2077: DNA324833, NM_014107, gen.NM_014107
Figure 2078: PRO81444
Figure 2079A-B: DNA324834, XM_084204, gen.XM_084204
Figure 2080: DNA324835, XM_017517, gen.XM_017517
Figure 2081: DNA324836, NM_032929, gen.NM_032929
Figure 2082: PRO81446
Figure 2083: DNA324837, XM_003611, gen.XM_003611
Figure 2084: PRO81447
Figure 2085: DNA324838, XM_068919, gen.XM_068919
Figure 2086: PRO81448
Figure 2087: DNA324839, XM_167016, gen.XM_167016
Figure 2088: PRO81449
Figure 2089: DNA324840, XM_087855, gen.XM_087855
Figure 2090: DNA324841, XM_087853, gen.XM_087853
Figure 2091: DNA324842, XM_165669, gen.XM_165669
Figure 2092: DNA324843, XM_166303, gen.XM_166303
Figure 2093: PRO81453
Figure 2094: DNA324844, XM_167027, gen.XM_167027
Figure 2095: PRO81454
Figure 2096: DNA324845, XM_167037, gen.XM_167037
Figure 2097: PRO81455
Figure 2098: DNA324846, XM_018182, gen.XM_018182
Figure 2099: DNA227924, NM_000165, gen.NM_000165
Figure 2100: PRO38387
Figure 2101: DNA324847, XM_166310, gen.XM_166310
Figure 2102: PRO81457
Figure 2103: DNA324848, XM_168054, gen.XM_168054
Figure 2104: DNA271418, NM_003287, gen.NM_003287
Figure 2105: PRO59717
Figure 2106: DNA324849, XM_114492, gen.XM_114492
Figure 2107: DNA324850, XM_037056, gen.XM_037056
Figure 2108: DNA324851, XM_098468, gen.XM_098468
Figure 2109: PRO19933
Figure 2110: DNA324852, XM_004526, gen.XM_004526
Figure 2111: DNA324853, NM_001016, gen.NM_001016
Figure 2112: PRO81462
Figure 2113: DNA324854, XM_004297, gen.XM_004297
Figure 2114: DNA324855, XM_004256, gen.XM_004256
Figure 2115: PRO81464
Figure 2116: DNA324856, NM_014320, gen.NM_014320
Figure 2117: PRO81465
Figure 2118: DNA324857, XM_059741, gen.XM_059741
Figure 2119: DNA324858, XM_017831, gen.XM_017831
Figure 2120: PRO81467

Figure 2121: DNA324859, XM_049899, gen.XM_049899
Figure 2122: DNA324860, XM_004379, gen.XM_004379
Figure 2123A-C: DNA324861, XM_087834, gen.XM_087834
Figure 2124A-B: DNA324862, XM_087836, gen.XM_087836
Figure 2125: PRO81471
Figure 2126: DNA324863, NM_005389, gen.NM_005389
Figure 2127: PRO66279
Figure 2128A-C: DNA324864, XM_029746, gen.XM_029746
Figure 2129: PRO66282
Figure 2130: DNA324865, XM_004383, gen.XM_004383
Figure 2131: DNA324866, XM_059745, gen.XM_059745
Figure 2132: DNA324867, XM_033912, gen.XM_033912
Figure 2133: PRO81474
Figure 2134: DNA324868, XM_033910, gen.XM_033910
Figure 2135: DNA324870, NM_003181, gen.NM_003181
Figure 2136: PRO81476
Figure 2137: DNA324871, NM_002793, gen.NM_002793
Figure 2138: PRO81477
Figure 2139: DNA324872, XM_044866, gen.XM_044866
Figure 2140: DNA324873, XM_116524, gen.XM_116524
Figure 2141: DNA324874, XM_059773, gen.XM_059773
Figure 2142: DNA324875, XM_084998, gen.XM_084998
Figure 2143: PRO81481
Figure 2144: DNA324876, XM_058266, gen.XM_058266
Figure 2145: DNA324877, XM_042422, gen.XM_042422
Figure 2146A-B: DNA324878, XM_054706, gen.XM_054706
Figure 2147: DNA324879, XM_166049, gen.XM_166049
Figure 2148: DNA324880, XM_042473, gen.XM_042473
Figure 2149: PRO81486
Figure 2150: DNA324881, XM_167046, gen.XM_167046
Figure 2151: PRO23797
Figure 2152: DNA324882, XM_071937, gen.XM_071937
Figure 2153: PRO81487

Figure 2154: DNA324883, XM_087991, gen.XM_087991
Figure 2155: DNA324884, NM_005514, gen.NM_005514
Figure 2156: PRO81490
Figure 2157: DNA324885, XM_166327, gen.XM_166327
Figure 2158: PRO81491
Figure 2159: DNA324886, XM_165692, gen.XM_165692
Figure 2160: DNA324887, XM_117449, gen.XM_117449
Figure 2161: DNA324888, XM_086428, gen.XM_086428
Figure 2162: PRO81494
Figure 2163: DNA324889, NM_032350, gen.NM_032350
Figure 2164: PRO81495
Figure 2165: DNA324890, NM_013393, gen.NM_013393
Figure 2166: PRO81496
Figure 2167: DNA324891, XM_165860, gen.XM_165860
Figure 2168: DNA324892, XM_166541, gen.XM_166541
Figure 2169: PRO81498
Figure 2170A-B: DNA324893, XM_166523, gen.XM_166523
Figure 2171: PRO81499
Figure 2172: DNA324894, NM_016003, gen.NM_016003
Figure 2173: PRO81500
Figure 2174: DNA225631, NM_001101, gen.NM_001101
Figure 2175: PRO36094
Figure 2176: DNA274326, NM_003088, gen.NM_003088
Figure 2177: PRO62244
Figure 2178: DNA324895, NM_006303, gen.NM_006303
Figure 2179: PRO81501
Figure 2180: DNA324896, NM_014413, gen.NM_014413
Figure 2181: PRO60579
Figure 2182: DNA247595, NM_006908, gen.NM_006908
Figure 2183: PRO45014
Figure 2184: DNA324897, NM_006854, gen.NM_006854
Figure 2185: PRO12468
Figure 2186: DNA324898, NM_024067, gen.NM_024067
Figure 2187: PRO81502
Figure 2188: DNA324899, NM_002947, gen.NM_002947
Figure 2189: PRO81503

Figure 2190: DNA324900, XM_166531, gen.XM_166531
Figure 2191: DNA324901, XM_166540, gen.XM_166540
Figure 2192: PRO81505
Figure 2193: DNA193955, NM_002489, gen.NM_002489
Figure 2194: PRO23362
Figure 2195: DNA324902, XM_088264, gen.XM_088264
Figure 2196: PRO81506
Figure 2197: DNA324903, XM_165841, gen.XM_165841
Figure 2198: DNA324904, XM_166521, gen.XM_166521
Figure 2199: PRO81508
Figure 2200: DNA324905, XM_166506, gen.XM_166506
Figure 2201: PRO81509
Figure 2202: DNA324906, XM_166505, gen.XM_166505
Figure 2203: DNA324907, XM_166514, gen.XM_166514
Figure 2204: DNA324908, XM_166515, gen.XM_166515
Figure 2205: DNA324909, XM_166512, gen.XM_166512
Figure 2206: DNA227929, NM_019059, gen.NM_019059
Figure 2207: PRO38392
Figure 2208A-B: DNA324910, NM_018947, gen.NM_018947
Figure 2209: PRO81514
Figure 2210: DNA324911, NM_002137, gen.NM_002137
Figure 2211: PRO81515
Figure 2212: DNA324912, NM_031243, gen.NM_031243
Figure 2213: PRO6373
Figure 2214: DNA324913, NM_007276, gen.NM_007276
Figure 2215: PRO81516
Figure 2216: DNA324914, NM_016587, gen.NM_016587
Figure 2217: PRO81517
Figure 2218: DNA324915, XM_040853, gen.XM_040853
Figure 2219: DNA324916, XM_166509, gen.XM_166509
Figure 2220: DNA324917, XM_166513, gen.XM_166513
Figure 2221: PRO81520
Figure 2222: DNA324918, XM_166504, gen.XM_166504
Figure 2223: PRO81521
Figure 2224: DNA324919, XM_166494, gen.XM_166494
Figure 2225: DNA324920, XM_107825, gen.XM_107825
Figure 2226A-B: DNA324921, NM_022748, gen.NM_022748
Figure 2227: PRO81523
Figure 2228: DNA324922, NM_000598, gen.NM_000598
Figure 2229: PRO119
Figure 2230A-B: DNA324923, XM_166594, gen.XM_166594
Figure 2231: PRO81524
Figure 2232A-B: DNA275334, NM_030900, gen.NM_030900
Figure 2233: PRO63009
Figure 2234: DNA324924, NM_031443, gen.NM_031443
Figure 2235: PRO81525
Figure 2236: DNA324925, NM_012412, gen.NM_012412
Figure 2237: PRO61812
Figure 2238: DNA324926, NM_021130, gen.NM_021130
Figure 2239: PRO7427
Figure 2240A-B: DNA324927, XM_165877, gen.XM_165877
Figure 2241: PRO81526
Figure 2242: DNA227268, NM_019082, gen.NM_019082
Figure 2243: PRO37731
Figure 2244: DNA324928, XM_015258, gen.XM_015258
Figure 2245: DNA324929, XM_165870, gen.XM_165870
Figure 2246: DNA273865, NM_006230, gen.NM_006230
Figure 2247: PRO61824
Figure 2248A-B: DNA324930, XM_165882, gen.XM_165882
Figure 2249: DNA324931, XM_165867, gen.XM_165867
Figure 2250: PRO61688
Figure 2251: DNA324932, NM_014063, gen.NM_014063
Figure 2252: PRO81529
Figure 2253: DNA324933, XM_165872, gen.XM_165872
Figure 2254: DNA304707, NM_002787, gen.NM_002787
Figure 2255: PRO71133
Figure 2256: DNA324934, XM_016733, gen.XM_016733
Figure 2257: PRO81531
Figure 2258: DNA324935, XM_165876, gen.XM_165876
Figure 2259A-B: DNA324936, NM_014800,

gen.NM_014800
Figure 2260: DNA324937, NM_130442, gen.NM_130442
Figure 2261: PRO81534
Figure 2262: DNA226416, NM_000385, gen.NM_000385
Figure 2263: PRO36879
Figure 2264A-B: DNA324938, XM_167339, gen.XM_167339
Figure 2265: DNA287189, NM_002047, gen.NM_002047
Figure 2266: PRO69475
Figure 2267: DNA324939, XM_170195, gen.XM_170195
Figure 2268: PRO81536
Figure 2269: DNA324940, XM_168378, gen.XM_168378
Figure 2270: PRO81537
Figure 2271: DNA324941, XM_168354, gen.XM_168354
Figure 2272: PRO81538
Figure 2273: DNA324942, XM_167494, gen.XM_167494
Figure 2274: DNA103588, NM_001762, gen.NM_001762
Figure 2275: PRO4912
Figure 2276: DNA324943, XM_037741, gen.XM_037741
Figure 2277: PRO81540
Figure 2278: DNA324944, XM_050265, gen.XM_050265
Figure 2279: PRO81541
Figure 2280: DNA324945, XM_017483, gen.XM_017483
Figure 2281A-B: DNA324946, XM_018359, gen.XM_018359
Figure 2282: DNA324947, XM_059876, gen.XM_059876
Figure 2283: PRO81544
Figure 2284: DNA324948, NM_032951, gen.NM_032951
Figure 2285: PRO81545
Figure 2286: DNA324949, NM_032953, gen.NM_032953
Figure 2287: PRO81546
Figure 2288: DNA324950, NM_022170, gen.NM_022170
Figure 2289: PRO81547
Figure 2290: DNA324951, NM_031992, gen.NM_031992
Figure 2291: PRO81548
Figure 2292: DNA324952, XM_004901, gen.XM_004901
Figure 2293: DNA324953, NM_016328, gen.NM_016328
Figure 2294: PRO81550
Figure 2295A-B: DNA324954, NM_032999, gen.NM_032999
Figure 2296: PRO81551
Figure 2297: DNA324955, XM_088239, gen.XM_088239
Figure 2298: PRO81552
Figure 2299A-B: DNA324956, XM_167500, gen.XM_167500
Figure 2300A-B: DNA324957, XM_167504, gen.XM_167504
Figure 2301: DNA324958, XM_167498, gen.XM_167498
Figure 2302: DNA324959, XM_168454, gen.XM_168454
Figure 2303: PRO81556
Figure 2304: DNA324960, NM_031925, gen.NM_031925
Figure 2305: PRO81557
Figure 2306: DNA324961, NM_005918, gen.NM_005918
Figure 2307: PRO81558
Figure 2308: DNA304710, NM_001540, gen.NM_001540
Figure 2309: PRO71136
Figure 2310: DNA324962, XM_168470, gen.XM_168470
Figure 2311: DNA324963, XM_168461, gen.XM_168461
Figure 2312A-B: DNA324964, XM_167502, gen.XM_167502
Figure 2313: DNA324965, XM_017442, gen.XM_017442
Figure 2314: PRO81561
Figure 2315: DNA324966, XM_168450, gen.XM_168450
Figure 2316: DNA324967, XM_168435, gen.XM_168435
Figure 2317: DNA324968, XM_168464, gen.XM_168464
Figure 2318: DNA324969, XM_170427, gen.XM_170427
Figure 2319A-B: DNA324971, NM_015068, gen.NM_015068
Figure 2320: PRO81566
Figure 2321A-B: DNA324972, XM_167476, gen.XM_167476
Figure 2322: DNA324973, XM_168181, gen.XM_168181
Figure 2323: DNA324974, XM_168251, gen.XM_168251
Figure 2324: PRO81569
Figure 2325: DNA324975, XM_167477, gen.XM_167477
Figure 2326: DNA324976, NM_005837, gen.NM_005837
Figure 2327: PRO81571

Figure 2328: DNA324977, XM_167483, gen.XM_167483
Figure 2329: DNA324978, XM_167484, gen.XM_167484
Figure 2330: PRO81572
Figure 2331: DNA324979, NM_030935, gen.NM_030935
Figure 2332: PRO81573
Figure 2333: DNA324980, NM_019606, gen.NM_019606
Figure 2334: PRO81574
Figure 2335: DNA324981, NM_024070, gen.NM_024070
Figure 2336: PRO81575
Figure 2337: DNA324982, XM_084241, gen.XM_084241
Figure 2338: DNA324983, NM_006833, gen.NM_006833
Figure 2339: PRO22897
Figure 2340: DNA324984, NM_032164, gen.NM_032164
Figure 2341: PRO81578
Figure 2342: DNA304801, NM_004889, gen.NM_004889
Figure 2343: PRO71211
Figure 2344: DNA324985, NM_006693, gen.NM_006693
Figure 2345: PRO81579
Figure 2346: DNA324986, XM_165839, gen.XM_165839
Figure 2347: PRO81580
Figure 2348: DNA272090, NM_005720, gen.NM_005720
Figure 2349: PRO60360
Figure 2350: DNA324987, XM_165836, gen.XM_165836
Figure 2351A-B: DNA324988, XM_166482, gen.XM_166482
Figure 2352: DNA324989, XM_088180, gen.XM_088180
Figure 2353A-B: DNA324990, XM_166485, gen.XM_166485
Figure 2354: PRO81584
Figure 2355: DNA324991, NM_001673, gen.NM_001673
Figure 2356: PRO81585
Figure 2357: DNA324992, NM_133436, gen.NM_133436
Figure 2358: PRO81586
Figure 2359: DNA324993, XM_168586, gen.XM_168586
Figure 2360: PRO81587
Figure 2361: DNA83141, NM_000602, gen.NM_000602
Figure 2362: PRO2604
Figure 2363: DNA324994, NM_057089, gen.NM_057089
Figure 2364: PRO81588
Figure 2365: DNA324995, NM_001283, gen.NM_001283
Figure 2366: PRO41882
Figure 2367: DNA324996, NM_003378, gen.NM_003378
Figure 2368: PRO81589
Figure 2369: DNA324997, NM_001084, gen.NM_001084
Figure 2370: PRO58437
Figure 2371: DNA270711, NM_006349, gen.NM_006349
Figure 2372: PRO59074
Figure 2373: DNA324998, NM_024653, gen.NM_024653
Figure 2374: PRO81590
Figure 2375: DNA324999, XM_168548, gen.XM_168548
Figure 2376: DNA325000, NM_032958, gen.NM_032958
Figure 2377: PRO81591
Figure 2378: DNA325001, NM_002803, gen.NM_002803
Figure 2379: PRO81592
Figure 2380: DNA325002, XM_168572, gen.XM_168572
Figure 2381: DNA325003, XM_071605, gen.XM_071605
Figure 2382: PRO81594
Figure 2383: DNA325004, XM_033876, gen.XM_033876
Figure 2384: PRO81595
Figure 2385A-B: DNA325005, XM_027214, gen.XM_027214
Figure 2386: DNA325006, XM_088073, gen.XM_088073
Figure 2387: DNA325007, XM_072430, gen.XM_072430
Figure 2388: PRO81598
Figure 2389: DNA325008, XM_050430, gen.XM_050430
Figure 2390: PRO81599
Figure 2391: DNA325009, NM_001753, gen.NM_001753
Figure 2392: PRO81600
Figure 2393: DNA226560, NM_006136, gen.NM_006136
Figure 2394: PRO37023
Figure 2395: DNA325010, XM_012284, gen.XM_012284
Figure 2396: DNA325011, NM_005000, gen.NM_005000
Figure 2397: PRO59380
Figure 2398: DNA325012, NM_001662, gen.NM_001662

Figure 2399: PRO39773
Figure 2400: DNA325013, XM_011618, gen.XM_011618
Figure 2401: PRO81602
Figure 2402: DNA325014, XM_004627, gen.XM_004627
Figure 2403: DNA325015, XM_045401, gen.XM_045401
Figure 2404: DNA325016, XM_114602, gen.XM_114602
Figure 2405: PRO81605
Figure 2406: DNA325017, XM_117481, gen.XM_117481
Figure 2407A-C: DNA325018, XM_045856, gen.XM_045856
Figure 2408: PRO81607
Figure 2409A-B: DNA325019, XM_088105, gen.XM_088105
Figure 2410: PRO81608
Figure 2411: DNA325020, XM_011548, gen.XM_011548
Figure 2412: PRO81609
Figure 2413: DNA325021, XM_045952, gen.XM_045952
Figure 2414: DNA325022, XM_046001, gen.XM_046001
Figure 2415: PRO81611
Figure 2416: DNA325023, XM_088099, gen.XM_088099
Figure 2417: DNA325024, XM_040498, gen.XM_040498
Figure 2418: DNA325025, XM_088103, gen.XM_088103
Figure 2419: PRO81614
Figure 2420: DNA325026, XM_088122, gen.XM_088122
Figure 2421: PRO81615
Figure 2422: DNA325027, XM_088119, gen.XM_088119
Figure 2423: DNA325028, NM_001628, gen.NM_001628
Figure 2424: PRO81617
Figure 2425: DNA325029, NM_020299, gen.NM_020299
Figure 2426: PRO81618
Figure 2427: DNA325030, NM_024033, gen.NM_024033
Figure 2428: PRO81619
Figure 2429: DNA325031, XM_114555, gen.XM_114555
Figure 2430: DNA325032, XM_059839, gen.XM_059839
Figure 2431: PRO81621
Figure 2432: DNA325033, XM_095146, gen.XM_095146
Figure 2433: DNA325034, XM_016700, gen.XM_016700
Figure 2434: DNA325035, XM_042781, gen.XM_042781
Figure 2435: DNA304685, NM_003143, gen.NM_003143
Figure 2436: PRO71111
Figure 2437: DNA325036, NM_018238, gen.NM_018238
Figure 2438: PRO81625
Figure 2439: DNA325037, XM_035107, gen.XM_035107
Figure 2440: DNA325038, NM_003461, gen.NM_003461
Figure 2441: PRO10194
Figure 2442: DNA325039, NM_004911, gen.NM_004911
Figure 2443: PRO2733
Figure 2444A-B: DNA325040, XM_114578, gen.XM_114578
Figure 2445: PRO81627
Figure 2446: DNA325041, XM_088135, gen.XM_088135
Figure 2447: DNA325042, XM_098654, gen.XM_098654
Figure 2448: PRO81629
Figure 2449: DNA325043, NM_023942, gen.NM_023942
Figure 2450: PRO81630
Figure 2451: DNA325044, NM_138434, gen.NM_138434
Figure 2452: PRO81631
Figure 2453: DNA325045, XM_084238, gen.XM_084238
Figure 2454A-B: DNA325046, XM_032216, gen.XM_032216
Figure 2455A-B: DNA325047, XM_032121, gen.XM_032121
Figure 2456: DNA325048, NM_031434, gen.NM_031434
Figure 2457: PRO1555
Figure 2458: DNA226337, NM_005692, gen.NM_005692
Figure 2459: PRO36800
Figure 2460: DNA325049, NM_005614, gen.NM_005614
Figure 2461: PRO37938
Figure 2462A-B: DNA325050, NM_053043, gen.NM_053043
Figure 2463: PRO81634
Figure 2464: DNA325051, NM_022458, gen.NM_022458
Figure 2465: PRO81635
Figure 2466: DNA325052, XM_098669, gen.XM_098669
Figure 2467: DNA325053, NM_017760, gen.NM_017760

Figure 2468: PRO81637
Figure 2469: DNA325054, XM_036413, gen.XM_036413
Figure 2470A-B: DNA325055, XM_032944, gen.XM_032944
Figure 2471: DNA325056, XM_117444, gen.XM_117444
Figure 2472: DNA325057, XM_117452, gen.XM_117452
Figure 2473: DNA325058, XM_070203, gen.XM_070203
Figure 2474: PRO81641
Figure 2475: DNA325059, XM_095371, gen.XM_095371
Figure 2476: DNA325060, NM_004084, gen.NM_004084
Figure 2477: PRO2570
Figure 2478: DNA325061, NM_005217, gen.NM_005217
Figure 2479: PRO9980
Figure 2480: DNA325062, XM_070188, gen.XM_070188
Figure 2481: PRO81643
Figure 2482: DNA325063, XM_035680, gen.XM_035680
Figure 2483: DNA325064, XM_035662, gen.XM_035662
Figure 2484: PRO3344
Figure 2485: DNA325065, XM_005305, gen.XM_005305
Figure 2486: PRO81645
Figure 2487: DNA325066, XM_050293, gen.XM_050293
Figure 2488A-B: DNA325067, XM_027679, gen.XM_027679
Figure 2489: PRO81647
Figure 2490A-B: DNA325068, XM_027651, gen.XM_027651
Figure 2491: DNA274178, NM_005775, gen.NM_005775
Figure 2492: PRO62108
Figure 2493: DNA325069, XM_113557, gen.XM_113557
Figure 2494: PRO81649
Figure 2495: DNA83022, NM_001199, gen.NM_001199
Figure 2496: PRO2042
Figure 2497: DNA325070, NM_006128, gen.NM_006128
Figure 2498: PRO81650
Figure 2499: DNA325071, NM_006131, gen.NM_006131
Figure 2500: PRO81651
Figure 2501: DNA325072, NM_006132, gen.NM_006132
Figure 2502: PRO81652
Figure 2503: DNA325073, NM_025232, gen.NM_025232
Figure 2504: PRO81653
Figure 2505: DNA325074, XM_027440, gen.XM_027440
Figure 2506: DNA225671, NM_001831, gen.NM_001831
Figure 2507: PRO36134
Figure 2508: DNA325075, NM_024567, gen.NM_024567
Figure 2509: PRO81654
Figure 2510: DNA325076, NM_018250, gen.NM_018250
Figure 2511: PRO81655
Figure 2512: DNA227267, NM_018660, gen.NM_018660
Figure 2513: PRO37730
Figure 2514A-B: DNA325077, XM_095545, gen.XM_095545
Figure 2515: DNA325078, XM_088338, gen.XM_088338
Figure 2516: PRO81657
Figure 2517: DNA325079, XM_114617, gen.XM_114617
Figure 2518: PRO81658
Figure 2519: DNA325080, XM_088336, gen.XM_088336
Figure 2520: PRO81659
Figure 2521: DNA325081, XM_047083, gen.XM_047083
Figure 2522: PRO81660
Figure 2523: DNA325082, XM_114618, gen.XM_114618
Figure 2524: PRO81661
Figure 2525: DNA325083, XM_050215, gen.XM_050215
Figure 2526: DNA325084, XM_113531, gen.XM_113531
Figure 2527: DNA325085, NM_018310, gen.NM_018310
Figure 2528: PRO81664
Figure 2529: DNA325086, XM_088294, gen.XM_088294
Figure 2530: DNA325087, XM_013112, gen.XM_013112
Figure 2531: DNA325088, XM_059933, gen.XM_059933
Figure 2532: PRO1108
Figure 2533: DNA325089, XM_011629, gen.XM_011629
Figure 2534: DNA325090, NM_000930, gen.NM_000930
Figure 2535: PRO4
Figure 2536: DNA325091, NM_000931, gen.NM_000931
Figure 2537: PRO81668

Figure 2538: DNA325092, NM_033011, gen.NM_033011

Figure 2539: PRO81669

Figure 2540: DNA325093, XM_166063, gen.XM_166063

Figure 2541: DNA325094, NM_025070, gen.NM_025070

Figure 2542: PRO81671

Figure 2543A-B: DNA325095, XM_030268, gen.XM_030268

Figure 2544: DNA325096, XM_030274, gen.XM_030274

Figure 2545: PRO81673

Figure 2546: DNA151010, NM_003350, gen.NM_003350

Figure 2547: PRO12838

Figure 2548: DNA325097, XM_113540, gen.XM_113540

Figure 2549: PRO81674

Figure 2550: DNA325098, NM_006330, gen.NM_006330

Figure 2551: PRO59230

Figure 2552: DNA325099, NM_001023, gen.NM_001023

Figure 2553: PRO58263

Figure 2554: DNA325100, XM_095667, gen.XM_095667

Figure 2555: PRO81675

Figure 2556: DNA325101, XM_114640, gen.XM_114640

Figure 2557: DNA325102, XM_057780, gen.XM_057780

Figure 2558: DNA325103, XM_166064, gen.XM_166064

Figure 2559: DNA325104, XM_088399, gen.XM_088399

Figure 2560: DNA325105, XM_088401, gen.XM_088401

Figure 2561: DNA325106, XM_042658, gen.XM_042658

Figure 2562: DNA325107, XM_011769, gen.XM_011769

Figure 2563: DNA325108, XM_044627, gen.XM_044627

Figure 2564: DNA325109, XM_098761, gen.XM_098761

Figure 2565: DNA226496, NM_006837, gen.NM_006837

Figure 2566: PRO36959

Figure 2567: DNA325110, NM_014294, gen.NM_014294

Figure 2568: PRO23248

Figure 2569: DNA325111, NM_000971, gen.NM_000971

Figure 2570: PRO81685

Figure 2571: DNA325112, XM_050731, gen.XM_050731

Figure 2572: DNA325113, XM_088325, gen.XM_088325

Figure 2573: PRO81687

Figure 2574: DNA325114, XM_088323, gen.XM_088323

Figure 2575: DNA325115, NM_001444, gen.NM_001444

Figure 2576: PRO81689

Figure 2577: DNA325116, XM_013127, gen.XM_013127

Figure 2578: PRO81690

Figure 2579: DNA325117, XM_165514, gen.XM_165514

Figure 2580: PRO81691

Figure 2581: DNA325118, XM_017816, gen.XM_017816

Figure 2582: DNA325119, XM_098747, gen.XM_098747

Figure 2583: DNA325120, XM_050506, gen.XM_050506

Figure 2584: DNA325121, NM_024613, gen.NM_024613

Figure 2585: PRO81695

Figure 2586: DNA325122, XM_011642, gen.XM_011642

Figure 2587: PRO81696

Figure 2588: DNA325123, NM_000989, gen.NM_000989

Figure 2589: PRO11265

Figure 2590: DNA325124, NM_003406, gen.NM_003406

Figure 2591: PRO71091

Figure 2592: DNA325125, XM_011657, gen.XM_011657

Figure 2593: DNA131588, NM_002568, gen.NM_002568

Figure 2594: PRO7445

Figure 2595: DNA325126, XM_018287, gen.XM_018287

Figure 2596: DNA325127, NM_001568, gen.NM_001568

Figure 2597: PRO81699

Figure 2598: DNA325128, NM_003756, gen.NM_003756

Figure 2599: PRO81700

Figure 2600A-B: DNA272050, NM_006265, gen.NM_006265

Figure 2601: PRO60321

Figure 2602: DNA325129, NM_052886, gen.NM_052886

Figure 2603: PRO81701

Figure 2604: DNA325130, XM_016047, gen.XM_016047

Figure 2605: DNA325131, XM_005060, gen.XM_005060

Figure 2606: DNA325132, NM_005005, gen.NM_005005
Figure 2607: PRO81704
Figure 2608: DNA325133, XM_037657, gen.XM_037657
Figure 2609: DNA325134, XM_029567, gen.XM_029567
Figure 2610: PRO81705
Figure 2611: DNA325135, XM_088316, gen.XM_088316
Figure 2612: DNA325136, XM_051298, gen.XM_051298
Figure 2613: DNA325137, XM_088370, gen.XM_088370
Figure 2614: DNA325138, NM_016647, gen.NM_016647
Figure 2615: PRO23201
Figure 2616: DNA325139, NM_052963, gen.NM_052963
Figure 2617: PRO81708
Figure 2618: DNA325140, XM_049247, gen.XM_049247
Figure 2619: DNA325141, XM_058968, gen.XM_058968
Figure 2620: DNA325143, NM_023078, gen.NM_023078
Figure 2621: PRO81711
Figure 2622: DNA325144, XM_117487, gen.XM_117487
Figure 2623: DNA325145, XM_049226, gen.XM_049226
Figure 2624: PRO81714
Figure 2625: DNA325146, XM_114613, gen.XM_114613
Figure 2626: DNA325147, XM_035368, gen.XM_035368
Figure 2627: DNA325148, XM_113532, gen.XM_113532
Figure 2628: DNA325149, XM_088321, gen.XM_088321
Figure 2629: DNA325150, XM_035373, gen.XM_035373
Figure 2630: PRO81719
Figure 2631: DNA325151, XM_035370, gen.XM_035370
Figure 2632: PRO81720
Figure 2633: DNA325152, NM_000973, gen.NM_000973
Figure 2634: PRO22907
Figure 2635: DNA325153, NM_033301, gen.NM_033301
Figure 2636: PRO22907
Figure 2637: DNA325154, XM_049421, gen.XM_049421
Figure 2638: DNA325155, XM_034640, gen.XM_034640
Figure 2639: PRO81722
Figure 2640: DNA325156, XM_088550, gen.XM_088550
Figure 2641: DNA325157, XM_088552, gen.XM_088552
Figure 2642: DNA325158, XM_088553, gen.XM_088553
Figure 2643: PRO81725
Figure 2644: DNA325159, XM_059979, gen.XM_059979
Figure 2645: DNA325160, XM_167558, gen.XM_167558
Figure 2646: DNA325161, XM_039654, gen.XM_039654
Figure 2647: DNA325162, XM_060006, gen.XM_060006
Figure 2648: PRO81729
Figure 2649: DNA325163, NM_001122, gen.NM_001122
Figure 2650: PRO81730
Figure 2651: DNA325164, NM_001010, gen.NM_001010
Figure 2652: PRO10824
Figure 2653: DNA325165, NM_058195, gen.NM_058195
Figure 2654: PRO81731
Figure 2655: DNA325166, NM_000077, gen.NM_000077
Figure 2656: PRO36693
Figure 2657: DNA325167, NM_058196, gen.NM_058196
Figure 2658: PRO81732
Figure 2659: DNA325168, XM_017931, gen.XM_017931
Figure 2660: DNA271847, NM_001539, gen.NM_001539
Figure 2661: PRO60127
Figure 2662: DNA270991, NM_004323, gen.NM_004323
Figure 2663: PRO59321
Figure 2664: DNA325169, NM_016410, gen.NM_016410
Figure 2665: PRO81734
Figure 2666: DNA325170, XM_005543, gen.XM_005543
Figure 2667: PRO38028
Figure 2668: DNA325171, NM_001842, gen.NM_001842
Figure 2669: PRO21481
Figure 2670: DNA226345, NM_005866, gen.NM_005866
Figure 2671: PRO36808
Figure 2672: DNA325172, XM_088563, gen.XM_088563
Figure 2673: DNA325173, XM_059998, gen.XM_059998

Figure 2674: PRO59579
Figure 2675: DNA325174, NM_013442, gen.NM_013442
Figure 2676: PRO9819
Figure 2677: DNA325175, XM_114661, gen.XM_114661
Figure 2678: PRO81736
Figure 2679: DNA325176, XM_048479, gen.XM_048479
Figure 2680: DNA290319, NM_003289, gen.NM_003289
Figure 2681: PRO70595
Figure 2682A-C: DNA325177, NM_006289, gen.NM_006289
Figure 2683: PRO81738
Figure 2684: DNA325178, XM_048518, gen.XM_048518
Figure 2685: PRO81739
Figure 2686: DNA325179, XM_048539, gen.XM_048539
Figure 2687: PRO81740
Figure 2688: DNA325180, XM_114662, gen.XM_114662
Figure 2689: DNA325181, NM_001833, gen.NM_001833
Figure 2690: PRO81742
Figure 2691: DNA227491, NM_007096, gen.NM_007096
Figure 2692: PRO37954
Figure 2693: DNA254771, NM_012203, gen.NM_012203
Figure 2694: PRO49869
Figure 2695: DNA89242, NM_000700, gen.NM_000700
Figure 2696: PRO2907
Figure 2697: DNA325182, XM_041020, gen.XM_041020
Figure 2698: PRO81743
Figure 2699: DNA325183, XM_114686, gen.XM_114686
Figure 2700: DNA325184, XM_088637, gen.XM_088637
Figure 2701: DNA287216, NM_021154, gen.NM_021154
Figure 2702: PRO69496
Figure 2703: DNA288247, NM_058179, gen.NM_058179
Figure 2704: PRO70011
Figure 2705: DNA325185, XM_071178, gen.XM_071178
Figure 2706: PRO81746
Figure 2707: DNA325186, XM_005490, gen.XM_005490
Figure 2708: DNA325187, NM_031263, gen.NM_031263
Figure 2709: PRO81748

Figure 2710: DNA325188, XM_018006, gen.XM_018006
Figure 2711: DNA325189, XM_017996, gen.XM_017996
Figure 2712: DNA325190, XM_016113, gen.XM_016113
Figure 2713: PRO81751
Figure 2714: DNA272655, NM_001827, gen.NM_001827
Figure 2715: PRO60781
Figure 2716A-B: DNA325191, NM_002161, gen.NM_002161
Figure 2717: PRO81752
Figure 2718A-B: DNA325192, NM_013417, gen.NM_013417
Figure 2719: PRO81753
Figure 2720A-B: DNA325193, XM_046863, gen.XM_046863
Figure 2721: PRO81754
Figure 2722: DNA325194, XM_046836, gen.XM_046836
Figure 2723: DNA275322, NM_003837, gen.NM_003837
Figure 2724: PRO63000
Figure 2725A-B: DNA325195, XM_098943, gen.XM_098943
Figure 2726: DNA325196, XM_016308, gen.XM_016308
Figure 2727: DNA325197, XM_005525, gen.XM_005525
Figure 2728: DNA325198, NM_003389, gen.NM_003389
Figure 2729: PRO81759
Figure 2730: DNA325199, NM_033219, gen.NM_033219
Figure 2731: PRO81760
Figure 2732: DNA325200, NM_006401, gen.NM_006401
Figure 2733: PRO81761
Figure 2734: DNA272213, NM_002486, gen.NM_002486
Figure 2735: PRO60475
Figure 2736: DNA325201, NM_001333, gen.NM_001333
Figure 2737: PRO81762
Figure 2738: DNA325202, XM_116818, gen.XM_116818
Figure 2739: PRO81763
Figure 2740: DNA254543, NM_006808, gen.NM_006808
Figure 2741: PRO49648
Figure 2742: DNA325203, XM_070873, gen.XM_070873
Figure 2743: PRO81764
Figure 2744: DNA325204, XM_042788, gen.XM_042788

Figure 2745: PRO81765
Figure 2746: DNA257309, NM_032342, gen.NM_032342
Figure 2747: PRO51901
Figure 2748: DNA325205, XM_088569, gen.XM_088569
Figure 2749: PRO81766
Figure 2750: DNA325206, XM_088571, gen.XM_088571
Figure 2751: DNA271722, NM_004697, gen.NM_004697
Figure 2752: PRO60006
Figure 2753: DNA325207, NM_017443, gen.NM_017443
Figure 2754: PRO81768
Figure 2755A-C: DNA325208, XM_005348, gen.XM_005348
Figure 2756: DNA325209, XM_114646, gen.XM_114646
Figure 2757: DNA325210, XM_038391, gen.XM_038391
Figure 2758: PRO81771
Figure 2759A-B: DNA325211, XM_045296, gen.XM_045296
Figure 2760: DNA325212, XM_005365, gen.XM_005365
Figure 2761: DNA289530, NM_004435, gen.NM_004435
Figure 2762: PRO70290
Figure 2763: DNA287271, NM_032799, gen.NM_032799
Figure 2764: PRO69542
Figure 2765: DNA325213, XM_026987, gen.XM_026987
Figure 2766: DNA325214, XM_026985, gen.XM_026985
Figure 2767: DNA225630, NM_016174, gen.NM_016174
Figure 2768: PRO36093
Figure 2769: DNA325215, XM_026968, gen.XM_026968
Figure 2770: PRO81775
Figure 2771: DNA325216, XM_026951, gen.XM_026951
Figure 2772: DNA325217, NM_025072, gen.NM_025072
Figure 2773: PRO33818
Figure 2774: DNA325218, XM_033424, gen.XM_033424
Figure 2775: DNA325219, NM_004957, gen.NM_004957
Figure 2776: PRO81778
Figure 2777: DNA325220, XM_033457, gen.XM_033457
Figure 2778A-B: DNA325221, XM_033460, gen.XM_033460
Figure 2779: PRO81780
Figure 2780: DNA325222, NM_000976, gen.NM_000976
Figure 2781: PRO62236
Figure 2782: DNA218841, NM_012098, gen.NM_012098
Figure 2783: PRO34473
Figure 2784A-B: DNA325223, XM_052725, gen.XM_052725
Figure 2785: PRO81781
Figure 2786: DNA325224, XM_011752, gen.XM_011752
Figure 2787: DNA325225, XM_026944, gen.XM_026944
Figure 2788: PRO81783
Figure 2789: DNA325226, XM_116806, gen.XM_116806
Figure 2790A-B: DNA325227, NM_005347, gen.NM_005347
Figure 2791: PRO81785
Figure 2792: DNA325228, NM_005833, gen.NM_005833
Figure 2793: PRO81786
Figure 2794: DNA325229, NM_007209, gen.NM_007209
Figure 2795: PRO61897
Figure 2796: DNA88350, NM_000177, gen.NM_000177
Figure 2797: PRO2758
Figure 2798A-B: DNA325230, XM_011749, gen.XM_011749
Figure 2799: DNA325231, XM_114679, gen.XM_114679
Figure 2800: DNA325232, XM_087041, gen.XM_087041
Figure 2801: DNA325233, XM_114678, gen.XM_114678
Figure 2802: DNA325234, XM_114677, gen.XM_114677
Figure 2803: DNA325235, XM_087038, gen.XM_087038
Figure 2804: DNA325236, XM_059637, gen.XM_059637
Figure 2805: PRO81792
Figure 2806: DNA325237, NM_000368, gen.NM_000368
Figure 2807: PRO60115
Figure 2808: DNA325238, XM_033385, gen.XM_033385
Figure 2809A-B: DNA325239, XM_033380, gen.XM_033380
Figure 2810: PRO81794
Figure 2811: DNA325240, XM_033362, gen.XM_033362
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Figure 2813: DNA325241, XM_059986,

gen.XM_059986
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Figure 2815A-B: DNA325242, XM_033361, gen.XM_033361
Figure 2816: PRO81797
Figure 2817A-B: DNA325243, XM_033360, gen.XM_033360
Figure 2818: DNA325244, XM_033359, gen.XM_033359
Figure 2819A-B: DNA325245, XM_033355, gen.XM_033355
Figure 2820: DNA325246, NM_014285, gen.NM_014285
Figure 2821: PRO81800
Figure 2822: DNA325247, NM_054012, gen.NM_054012
Figure 2823: PRO81801
Figure 2824: DNA325248, XM_035103, gen.XM_035103
Figure 2825: DNA325249, XM_035109, gen.XM_035109
Figure 2826: DNA325250, NM_000972, gen.NM_000972
Figure 2827: PRO81804
Figure 2828: DNA325251, NM_033161, gen.NM_033161
Figure 2829: PRO81805
Figure 2830: DNA325252, NM_000787, gen.NM_000787
Figure 2831: PRO81806
Figure 2832A-B: DNA325253, XM_011778, gen.XM_011778
Figure 2833: DNA325254, XM_088426, gen.XM_088426
Figure 2834: DNA325255, NM_002003, gen.NM_002003
Figure 2835: PRO1910
Figure 2836: DNA325256, NM_058199, gen.NM_058199
Figure 2837: PRO81809
Figure 2838: DNA325257, XM_059945, gen.XM_059945
Figure 2839: DNA325258, XM_088422, gen.XM_088422
Figure 2840: PRO81811
Figure 2841: DNA325259, XM_029168, gen.XM_029168
Figure 2842: PRO81812
Figure 2843: DNA325260, XM_098913, gen.XM_098913
Figure 2844: PRO81813
Figure 2845: DNA325261, XM_114669, gen.XM_114669
Figure 2846: DNA325262, XM_113564, gen.XM_113564
Figure 2847A-B: DNA325263, XM_088459,

gen.XM_088459
Figure 2848: PRO81815
Figure 2849: DNA325264, XM_054752, gen.XM_054752
Figure 2850: PRO81816
Figure 2851: DNA325265, XM_084270, gen.XM_084270
Figure 2852: DNA325266, XM_054763, gen.XM_054763
Figure 2853: PRO81817
Figure 2854: DNA325267, XM_114655, gen.XM_114655
Figure 2855: DNA325268, XM_038030, gen.XM_038030
Figure 2856: PRO59351
Figure 2857: DNA325269, XM_072526, gen.XM_072526
Figure 2858: PRO81819
Figure 2859: DNA325270, XM_059961, gen.XM_059961
Figure 2860: DNA325271, NM_032928, gen.NM_032928
Figure 2861: PRO81821
Figure 2862: DNA325272, NM_014172, gen.NM_014172
Figure 2863: PRO81822
Figure 2864: DNA325273, XM_038049, gen.XM_038049
Figure 2865: PRO62069
Figure 2866: DNA325274, XM_038063, gen.XM_038063
Figure 2867: PRO81823
Figure 2868: DNA325275, NM_000954, gen.NM_000954
Figure 2869: PRO81824
Figure 2870: DNA325276, XM_088461, gen.XM_088461
Figure 2871: DNA325277, XM_059966, gen.XM_059966
Figure 2872: PRO81826
Figure 2873: DNA325278, XM_114649, gen.XM_114649
Figure 2874: DNA325279, XM_117519, gen.XM_117519
Figure 2875: DNA325280, XM_053206, gen.XM_053206
Figure 2876: DNA325281, XM_040272, gen.XM_040272
Figure 2877: PRO58939
Figure 2878: DNA325282, XM_005724, gen.XM_005724
Figure 2879: DNA325283, XM_040267, gen.XM_040267
Figure 2880: PRO81831
Figure 2881: DNA325284, XM_048859, gen.XM_048859

Figure 2882: PRO62617
Figure 2883: DNA325285, NM_003739, gen.NM_003739
Figure 2884: PRO81832
Figure 2885: DNA325286, XM_060976, gen.XM_060976
Figure 2886: PRO81833
Figure 2887: DNA325287, XM_167626, gen.XM_167626
Figure 2888: PRO81834
Figure 2889: DNA325288, XM_165555, gen.XM_165555
Figure 2890: PRO81835
Figure 2891: DNA325289, NM_001494, gen.NM_001494
Figure 2892: PRO81836
Figure 2893: DNA325290, NM_032905, gen.NM_032905
Figure 2894: PRO81837
Figure 2895: DNA325291, NM_005174, gen.NM_005174
Figure 2896: PRO81838
Figure 2897: DNA325292, XM_165557, gen.XM_165557
Figure 2898: DNA325293, XM_167374, gen.XM_167374
Figure 2899: DNA273759, NM_006023, gen.NM_006023
Figure 2900: PRO61721
Figure 2901: DNA325294, XM_167411, gen.XM_167411
Figure 2902: DNA325295, NM_031453, gen.NM_031453
Figure 2903: PRO81841
Figure 2904: DNA325296, XM_167414, gen.XM_167414
Figure 2905: PRO12851
Figure 2906: DNA325297, XM_166717, gen.XM_166717
Figure 2907: PRO81842
Figure 2908: DNA325298, XM_005100, gen.XM_005100
Figure 2909: DNA325299, XM_038536, gen.XM_038536
Figure 2910A-B: DNA325300, XM_084420, gen.XM_084420
Figure 2911: DNA325301, XM_084429, gen.XM_084429
Figure 2912: PRO81846
Figure 2913A-C: DNA325302, XM_165551, gen.XM_165551
Figure 2914: DNA325303, XM_059720, gen.XM_059720
Figure 2915: PRO81848
Figure 2916A-B: DNA325304, NM_019619, gen.NM_019619

Figure 2917: PRO81849
Figure 2918: DNA325305, XM_166665, gen.XM_166665
Figure 2919A-B: DNA325306, NM_002211, gen.NM_002211
Figure 2920: PRO81851
Figure 2921A-B: DNA325307, XM_165567, gen.XM_165567
Figure 2922: DNA325308, XM_166157, gen.XM_166157
Figure 2923: DNA325309, NM_032023, gen.NM_032023
Figure 2924: PRO52537
Figure 2925: DNA325310, XM_165560, gen.XM_165560
Figure 2926: DNA325311, XM_165563, gen.XM_165563
Figure 2927: DNA325312, XM_113615, gen.XM_113615
Figure 2928: PRO81855
Figure 2929: DNA325313, XM_165890, gen.XM_165890
Figure 2930: DNA325314, XM_061126, gen.XM_061126
Figure 2931: DNA325315, XM_061125, gen.XM_061125
Figure 2932: PRO81858
Figure 2933: DNA325316, XM_054474, gen.XM_054474
Figure 2934: DNA325317, XM_165888, gen.XM_165888
Figure 2935: DNA325318, XM_054475, gen.XM_054475
Figure 2936: PRO81861
Figure 2937: DNA325319, XM_015652, gen.XM_015652
Figure 2938: PRO81862
Figure 2939: DNA325320, XM_036593, gen.XM_036593
Figure 2940: PRO81863
Figure 2941: DNA325321, XM_165891, gen.XM_165891
Figure 2942: DNA325322, XM_084450, gen.XM_084450
Figure 2943: PRO81865
Figure 2944: DNA325323, XM_084385, gen.XM_084385
Figure 2945: DNA325324, NM_021226, gen.NM_021226
Figure 2946: PRO81867
Figure 2947: DNA193957, NM_003055, gen.NM_003055
Figure 2948: PRO23364
Figure 2949: DNA325325, NM_032997, gen.NM_032997
Figure 2950: PRO81868

Figure 2951: DNA287642, NM_018464, gen.NM_018464
Figure 2952: PRO9902
Figure 2953: DNA325326, XM_084451, gen.XM_084451
Figure 2954: PRO81869
Figure 2955: DNA325327, NM_012207, gen.NM_012207
Figure 2956: PRO81870
Figure 2957: DNA325328, NM_024045, gen.NM_024045
Figure 2958: PRO81871
Figure 2959: DNA325329, NM_004728, gen.NM_004728
Figure 2960: PRO81872
Figure 2961: DNA88562, NM_002727, gen.NM_002727
Figure 2962: PRO2842
Figure 2963: DNA325330, XM_167395, gen.XM_167395
Figure 2964: DNA227172, NM_021129, gen.NM_021129
Figure 2965: PRO37635
Figure 2966A-B: DNA325331, XM_166125, gen.XM_166125
Figure 2967: PRO81874
Figure 2968: DNA325332, XM_044354, gen.XM_044354
Figure 2969: PRO81875
Figure 2970: DNA325333, XM_032520, gen.XM_032520
Figure 2971: DNA325334, NM_019058, gen.NM_019058
Figure 2972: PRO81877
Figure 2973: DNA325335, XM_045140, gen.XM_045140
Figure 2974: PRO2875
Figure 2975: DNA325336, XM_116863, gen.XM_116863
Figure 2976: DNA325337, XM_032476, gen.XM_032476
Figure 2977: DNA325338, XM_114894, gen.XM_114894
Figure 2978: DNA325339, NM_033022, gen.NM_033022
Figure 2979: PRO81881
Figure 2980: DNA325340, NM_001026, gen.NM_001026
Figure 2981: PRO11139
Figure 2982: DNA103421, NM_003375, gen.NM_003375
Figure 2983: PRO4749
Figure 2984A-B: DNA325341, XM_166093, gen.XM_166093
Figure 2985: PRO81882
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Figure 2990: DNA103506, NM_001157, gen.NM_001157
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Figure 2994: DNA325344, XM_084467, gen.XM_084467
Figure 2995: PRO81885
Figure 2996: DNA304488, NM_032333, gen.NM_032333
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Figure 2998: DNA325345, XM_043589, gen.XM_043589
Figure 2999: DNA325346, XM_043605, gen.XM_043605
Figure 3000: DNA325347, XM_087480, gen.XM_087480
Figure 3001: PRO81887
Figure 3002: DNA325348, NM_002921, gen.NM_002921
Figure 3003: PRO81888
Figure 3004: DNA226217, NM_005271, gen.NM_005271
Figure 3005: PRO36680
Figure 3006: DNA325349, XM_089551, gen.XM_089551
Figure 3007: PRO81889
Figure 3008: DNA287237, NM_001613, gen.NM_001613
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Figure 3010: DNA325350, XM_084477, gen.XM_084477
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Figure 3012: DNA325351, XM_084480, gen.XM_084480
Figure 3013A-B: DNA325352, NM_013451, gen.NM_013451
Figure 3014: PRO12813
Figure 3015: DNA325353, XM_018167, gen.XM_018167
Figure 3016: DNA325354, XM_084372, gen.XM_084372
Figure 3017: DNA325355, NM_020992, gen.NM_020992
Figure 3018: PRO81893
Figure 3019: DNA325356, XM_089514, gen.XM_089514
Figure 3020A-B: DNA325357, XM_058343, gen.XM_058343
Figure 3021: PRO81895

Figure 3022: DNA325358, XM_058602, gen.XM_058602

Figure 3023: PRO81896

Figure 3024A-B: DNA325359, NM_015179, gen.NM_015179

Figure 3025: PRO81897

Figure 3026: DNA325360, XM_083842, gen.XM_083842

Figure 3027: PRO69473

Figure 3028: DNA325361, XM_084413, gen.XM_084413

Figure 3029: DNA325362, NM_022362, gen.NM_022362

Figure 3030: PRO81899

Figure 3031: DNA325363, NM_032112, gen.NM_032112

Figure 3032: PRO81900

Figure 3033: DNA325364, NM_021830, gen.NM_021830

Figure 3034: PRO81901

Figure 3035A-B: DNA325365, XM_046743, gen.XM_046743

Figure 3036: PRO81902

Figure 3037: DNA325366, NM_013274, gen.NM_013274

Figure 3038: PRO81903

Figure 3039: DNA325367, NM_022039, gen.NM_022039

Figure 3040: PRO81904

Figure 3041A-B: DNA325368, XM_031866, gen.XM_031866

Figure 3042A-B: DNA325369, NM_015062, gen.NM_015062

Figure 3043: PRO81905

Figure 3044A-B: DNA325370, XM_031890, gen.XM_031890

Figure 3045A-B: DNA325371, NM_004193, gen.NM_004193

Figure 3046: PRO81907

Figure 3047: DNA325372, NM_024040, gen.NM_024040

Figure 3048: PRO81908

Figure 3049: DNA325373, XM_031949, gen.XM_031949

Figure 3050: PRO4900

Figure 3051A-B: DNA144601, NM_016169, gen.NM_016169

Figure 3052: PRO34073

Figure 3053: DNA325374, XM_005698, gen.XM_005698

Figure 3054: PRO81909

Figure 3055: DNA325375, NM_006523, gen.NM_006523

Figure 3056: PRO59043

Figure 3057: DNA325376, XM_018279, gen.XM_018279

Figure 3058A-B: DNA325377, XM_005938, gen.XM_005938

Figure 3059A-B: DNA325378, XM_031992, gen.XM_031992

Figure 3060: PRO81912

Figure 3061: DNA325379, NM_032747, gen.NM_032747

Figure 3062: PRO81913

Figure 3063: DNA325380, NM_005004, gen.NM_005004

Figure 3064: PRO81914

Figure 3065: DNA325381, XM_030447, gen.XM_030447

Figure 3066: DNA273521, NM_002079, gen.NM_002079

Figure 3067: PRO61502

Figure 3068A-B: DNA325382, NM_032211, gen.NM_032211

Figure 3069: PRO81916

Figure 3070: DNA325383, NM_031484, gen.NM_031484

Figure 3071: PRO81917

Figure 3072: DNA325384, XM_084632, gen.XM_084632

Figure 3073: DNA325385, XM_084359, gen.XM_084359

Figure 3074A-D: DNA325386, XM_045667, gen.XM_045667

Figure 3075: DNA325387, XM_109162, gen.XM_109162

Figure 3076: DNA227509, NM_000274, gen.NM_000274

Figure 3077: PRO37972

Figure 3078: DNA325388, XM_058361, gen.XM_058361

Figure 3079: PRO81922

Figure 3080: DNA325389, XM_084505, gen.XM_084505

Figure 3081: PRO81923

Figure 3082A-B: DNA325390, XM_049795, gen.XM_049795

Figure 3083: PRO81924

Figure 3084: DNA325391, XM_058406, gen.XM_058406

Figure 3085: PRO81925

Figure 3086: DNA325392, XM_055573, gen.XM_055573

Figure 3087: PRO60991

Figure 3088: DNA325393, XM_005969, gen.XM_005969

Figure 3089: DNA325394, NM_007190, gen.NM_007190

Figure 3090: PRO81926

Figure 3091: DNA325395, NM_000982, gen.NM_000982

Figure 3092: PRO81927

Figure 3093: DNA269952, NM_004725, gen.NM_004725
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Figure 3095: DNA325396, NM_024942, gen.NM_024942
Figure 3096: PRO81928
Figure 3097: DNA325397, NM_016567, gen.NM_016567
Figure 3098: PRO81929
Figure 3099: DNA325398, NM_004092, gen.NM_004092
Figure 3100: PRO81930
Figure 3101: DNA269431, NM_006659, gen.NM_006659
Figure 3102: PRO57854
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Figure 3104: DNA325400, XM_114862, gen.XM_114862
Figure 3105: PRO81932
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Figure 3107: DNA325402, NM_016526, gen.NM_016526
Figure 3108: PRO81934
Figure 3109: DNA255696, NM_021932, gen.NM_021932
Figure 3110: PRO50756
Figure 3111: DNA325403, XM_043220, gen.XM_043220
Figure 3112: PRO81935
Figure 3113: DNA255078, NM_006435, gen.NM_006435
Figure 3114: PRO50165
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Figure 3116: PRO81936
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Figure 3119: DNA325406, XM_096544, gen.XM_096544
Figure 3120: DNA325407, NM_000612, gen.NM_000612
Figure 3121: PRO124
Figure 3122: DNA325408, XM_084742, gen.XM_084742
Figure 3123: PRO81939
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Figure 3125: DNA325410, XM_058505, gen.XM_058505
Figure 3126: PRO81941
Figure 3127: DNA325411, XM_006139, gen.XM_006139
Figure 3128: PRO81942

Figure 3129: DNA325412, XM_044932, gen.XM_044932
Figure 3130: PRO81943
Figure 3131A-B: DNA325413, XM_044957, gen.XM_044957
Figure 3132: PRO81944
Figure 3133: DNA325414, NM_001909, gen.NM_001909
Figure 3134: PRO292
Figure 3135: DNA325415, XM_006475, gen.XM_006475
Figure 3136: DNA325416, XM_006483, gen.XM_006483
Figure 3137: DNA325417, NM_001751, gen.NM_001751
Figure 3138: PRO69635
Figure 3139: DNA325418, XM_114981, gen.XM_114981
Figure 3140: PRO81945
Figure 3141: DNA325419, XM_083852, gen.XM_083852
Figure 3142: DNA325420, NM_000559, gen.NM_000559
Figure 3143: PRO81946
Figure 3144: DNA325421, NM_000184, gen.NM_000184
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Figure 3146: DNA325422, NM_005330, gen.NM_005330
Figure 3147: PRO81948
Figure 3148: DNA325423, XM_015243, gen.XM_015243
Figure 3149: DNA325424, NM_015324, gen.NM_015324
Figure 3150: PRO81950
Figure 3151: DNA325425, XM_006424, gen.XM_006424
Figure 3152: DNA325426, XM_113238, gen.XM_113238
Figure 3153A-C: DNA325427, XM_052786, gen.XM_052786
Figure 3154: PRO81953
Figure 3155: DNA325428, NM_000990, gen.NM_000990
Figure 3156: PRO25985
Figure 3157A-B: DNA325429, XM_045750, gen.XM_045750
Figure 3158: PRO81954
Figure 3159: DNA325430, XM_058414, gen.XM_058414
Figure 3160: PRO81955
Figure 3161A-B: DNA325431, XM_049197, gen.XM_049197
Figure 3162: PRO81956
Figure 3163A-B: DNA325432, NM_001418, gen.NM_001418

Figure 3164: PRO81957
Figure 3165: DNA325433, XM_096520, gen.XM_096520
Figure 3166: PRO81958
Figure 3167: DNA325434, XM_006212, gen.XM_006212
Figure 3168: PRO81959
Figure 3169: DNA325435, XM_084527, gen.XM_084527
Figure 3170: DNA325436, XM_016139, gen.XM_016139
Figure 3171: DNA325437, NM_001017, gen.NM_001017
Figure 3172: PRO11262
Figure 3173: DNA325438, NM_014267, gen.NM_014267
Figure 3174: PRO81962
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Figure 3177: DNA325439, XM_115081, gen.XM_115081
Figure 3178: DNA325440, XM_036339, gen.XM_036339
Figure 3179: PRO81964
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Figure 3181: PRO81965
Figure 3182: DNA325442, XM_084516, gen.XM_084516
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Figure 3184: DNA325444, XM_084517, gen.XM_084517
Figure 3185: DNA325445, XM_034431, gen.XM_034431
Figure 3186: PRO11691
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Figure 3189: PRO81970
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Figure 3195: DNA325452, XM_084681, gen.XM_084681
Figure 3196: DNA325453, XM_006297, gen.XM_006297
Figure 3197: DNA325454, NM_003646, gen.NM_003646
Figure 3198: PRO81977
Figure 3199: DNA325455, NM_004551, gen.NM_004551
Figure 3200: PRO81978
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Figure 3203: PRO81980
Figure 3204: DNA150974, NM_005693, gen.NM_005693
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Figure 3206: DNA226080, NM_001610, gen.NM_001610
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Figure 3209: PRO58523
Figure 3210: DNA325458, NM_016223, gen.NM_016223
Figure 3211: PRO81981
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Figure 3214: DNA325460, XM_015705, gen.XM_015705
Figure 3215: DNA272728, NM_003146, gen.NM_003146
Figure 3216: PRO60847
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Figure 3218: DNA287417, NM_024098, gen.NM_024098
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Figure 3220: DNA227088, NM_014502, gen.NM_014502
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Figure 3223A-B: DNA325463, XM_165612, gen.XM_165612
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Figure 3226: PRO81988
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Figure 3228A-B: DNA325467, XM_167748, gen.XM_167748
Figure 3229: PRO81990
Figure 3230: DNA325468, NM_004739, gen.NM_004739
Figure 3231: PRO81991
Figure 3232: DNA325469, NM_014610,

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Figure 3233: PRO81992
Figure 3234: DNA325470, XM_167747, gen.XM_167747
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Figure 3244: DNA325474, XM_167716, gen.XM_167716
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Figure 3247: DNA325475, XM_087710, gen.XM_087710
Figure 3248: DNA325476, XM_167726, gen.XM_167726
Figure 3249: DNA325477, NM_004265, gen.NM_004265
Figure 3250: PRO12878
Figure 3251A-B: DNA325478, NM_013402, gen.NM_013402
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Figure 3255: DNA325480, XM_048286, gen.XM_048286
Figure 3256: DNA325481, NM_004322, gen.NM_004322
Figure 3257: PRO20117
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Figure 3260: DNA325483, XM_011988, gen.XM_011988
Figure 3261: DNA325484, NM_031472, gen.NM_031472
Figure 3262: PRO82002
Figure 3263: DNA325485, XM_037808, gen.XM_037808
Figure 3264: DNA325486, NM_004074, gen.NM_004074
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Figure 3267: PRO82005

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Figure 3269: DNA325489, XM_045642, gen.XM_045642
Figure 3270: DNA325490, XM_006533, gen.XM_006533
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Figure 3273A-B: DNA325492, XM_045612, gen.XM_045612
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Figure 3275: DNA325493, XM_113224, gen.XM_113224
Figure 3276: DNA325494, XM_045499, gen.XM_045499
Figure 3277: PRO82011
Figure 3278: DNA325495, XM_045525, gen.XM_045525
Figure 3279: DNA325496, NM_013265, gen.NM_013265
Figure 3280: PRO82013
Figure 3281: DNA325497, XM_006529, gen.XM_006529
Figure 3282: PRO60008
Figure 3283: DNA325498, XM_053787, gen.XM_053787
Figure 3284: DNA269803, NM_001667, gen.NM_001667
Figure 3285: PRO58207
Figure 3286: DNA325499, XM_115031, gen.XM_115031
Figure 3287: DNA325500, XM_084702, gen.XM_084702
Figure 3288: DNA325501, XM_053796, gen.XM_053796
Figure 3289: DNA325502, NM_002689, gen.NM_002689
Figure 3290: PRO82018
Figure 3291A-D: DNA325503, XM_167804, gen.XM_167804
Figure 3292: PRO82019
Figure 3293: DNA325504, XM_166235, gen.XM_166235
Figure 3294: DNA325505, XM_166236, gen.XM_166236
Figure 3295: DNA270721, NM_006842, gen.NM_006842
Figure 3296: PRO59084
Figure 3297: DNA189687, NM_000852, gen.NM_000852
Figure 3298: PRO25845
Figure 3299: DNA325506, NM_007103, gen.NM_007103
Figure 3300: PRO58606
Figure 3301: DNA325507, NM_005851,

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Figure 3302: PRO69461
Figure 3303A-B: DNA325508, XM_165598, gen.XM_165598
Figure 3304: DNA325509, NM_006019, gen.NM_006019
Figure 3305: PRO82023
Figure 3306: DNA325510, NM_006053, gen.NM_006053
Figure 3307: PRO24831
Figure 3308: DNA325511, XM_166196, gen.XM_166196
Figure 3309: PRO82024
Figure 3310: DNA325512, XM_165600, gen.XM_165600
Figure 3311A-B: DNA325513, NM_053056, gen.NM_053056
Figure 3312: PRO4870
Figure 3313: DNA103474, NM_003824, gen.NM_003824
Figure 3314: PRO4801
Figure 3315: DNA325514, XM_096486, gen.XM_096486
Figure 3316A-B: DNA325515, NM_003626, gen.NM_003626
Figure 3317: PRO82027
Figure 3318A-B: DNA325516, XM_167853, gen.XM_167853
Figure 3319: PRO82028
Figure 3320: DNA325517, NM_014042, gen.NM_014042
Figure 3321: PRO82029
Figure 3322A-B: DNA325518, NM_001567, gen.NM_001567
Figure 3323: PRO61238
Figure 3324: DNA325519, XM_167433, gen.XM_167433
Figure 3325: DNA325520, XM_165616, gen.XM_165616
Figure 3326: DNA325521, NM_032871, gen.NM_032871
Figure 3327: PRO57307
Figure 3328: DNA325522, XM_165631, gen.XM_165631
Figure 3329: DNA254186, NM_014752, gen.NM_014752
Figure 3330: PRO49298
Figure 3331: DNA325523, NM_001005, gen.NM_001005
Figure 3332: PRO82032
Figure 3333: DNA88176, NM_001235, gen.NM_001235
Figure 3334: PRO2685
Figure 3335A-B: DNA325524, XM_165627, gen.XM_165627
Figure 3336: DNA325525, XM_166253, gen.XM_166253
Figure 3337: DNA325526, NM_001293, gen.NM_001293
Figure 3338: PRO82034
Figure 3339: DNA325527, XM_042852, gen.XM_042852
Figure 3340: PRO82035
Figure 3341: DNA325528, XM_165628, gen.XM_165628
Figure 3342A-B: DNA325529, NM_080491, gen.NM_080491
Figure 3343: PRO82037
Figure 3344A-B: DNA325530, NM_012296, gen.NM_012296
Figure 3345: PRO60311
Figure 3346: DNA325531, NM_032379, gen.NM_032379
Figure 3347: PRO82038
Figure 3348: DNA325532, NM_007173, gen.NM_007173
Figure 3349: DNA325533, XM_166239, gen.XM_166239
Figure 3350: DNA325534, XM_084610, gen.XM_084610
Figure 3351: PRO82040
Figure 3352: DNA325535, XM_058450, gen.XM_058450
Figure 3353: DNA325536, XM_084601, gen.XM_084601
Figure 3354: PRO82042
Figure 3355A-B: DNA325537, XM_006464, gen.XM_006464
Figure 3356: PRO82043
Figure 3357: DNA325538, XM_084570, gen.XM_084570
Figure 3358: DNA325539, XM_051435, gen.XM_051435
Figure 3359: DNA325540, NM_001467, gen.NM_001467
Figure 3360: PRO82045
Figure 3361: DNA325541, NM_001028, gen.NM_001028
Figure 3362: PRO82046
Figure 3363: DNA325542, XM_113230, gen.XM_113230
Figure 3364: DNA325543, XM_115062, gen.XM_115062
Figure 3365: DNA325544, XM_115063, gen.XM_115063
Figure 3366: DNA325545, XM_113229, gen.XM_113229
Figure 3367A-B: DNA325546, XM_051489, gen.XM_051489
Figure 3368: PRO82050
Figure 3369: DNA325547, NM_022003, gen.NM_022003

Figure 3370: PRO82051
Figure 3371: DNA325548, XM_006432, gen.XM_006432
Figure 3372: PRO82052
Figure 3373: DNA325549, XM_051716, gen.XM_051716
Figure 3374: DNA325550, NM_025164, gen.NM_025164
Figure 3375: PRO82054
Figure 3376: DNA225752, NM_000039, gen.NM_000039
Figure 3377: PRO36215
Figure 3378: DNA325551, XM_052113, gen.XM_052113
Figure 3379: PRO82055
Figure 3380: DNA271324, NM_006169, gen.NM_006169
Figure 3381: PRO59629
Figure 3382: DNA325552, XM_084658, gen.XM_084658
Figure 3383: PRO82056
Figure 3384: DNA325553, NM_000795, gen.NM_000795
Figure 3385: PRO12448
Figure 3386: DNA325554, NM_017868, gen.NM_017868
Figure 3387: PRO82057
Figure 3388: DNA325555, XM_084654, gen.XM_084654
Figure 3389: PRO82058
Figure 3390: DNA272413, NM_003002, gen.NM_003002
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Figure 3392: DNA271843, NM_004398, gen.NM_004398
Figure 3393: PRO60123
Figure 3394: DNA325556, XM_017369, gen.XM_017369
Figure 3395: DNA325557, NM_032299, gen.NM_032299
Figure 3396: PRO82060
Figure 3397: DNA325558, XM_055369, gen.XM_055369
Figure 3398: DNA325559, XM_051430, gen.XM_051430
Figure 3399: DNA325560, XM_006467, gen.XM_006467
Figure 3400: DNA325561, XM_113226, gen.XM_113226
Figure 3401: DNA325562, XM_165592, gen.XM_165592
Figure 3402: PRO82064
Figure 3403: DNA325563, XM_166181, gen.XM_166181
Figure 3404: DNA325564, XM_052862, gen.XM_052862
Figure 3405: PRO82066
Figure 3406: DNA325565, XM_166177, gen.XM_166177
Figure 3407: DNA325566, XM_165571, gen.XM_165571
Figure 3408: PRO82068
Figure 3409: DNA325567, XM_166174, gen.XM_166174
Figure 3410: PRO82069
Figure 3411: DNA325568, NM_001274, gen.NM_001274
Figure 3412: PRO12187
Figure 3413: DNA325569, XM_165586, gen.XM_165586
Figure 3414: DNA325570, XM_165584, gen.XM_165584
Figure 3415: DNA257965, NM_032873, gen.NM_032873
Figure 3416: PRO52492
Figure 3417: DNA325571, XM_167780, gen.XM_167780
Figure 3418: DNA325572, XM_166743, gen.XM_166743
Figure 3419: PRO82072
Figure 3420: DNA325573, NM_012101, gen.NM_012101
Figure 3421: PRO82073
Figure 3422: DNA325574, NM_058193, gen.NM_058193
Figure 3423: PRO82074
Figure 3424: DNA325575, XM_084522, gen.XM_084522
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Figure 3426: DNA325576, XM_091786, gen.XM_091786
Figure 3427: DNA325577, XM_165390, gen.XM_165390
Figure 3428: DNA325578, XM_084525, gen.XM_084525
Figure 3429A-B: DNA325579, XM_010494, gen.XM_010494
Figure 3430A-B: DNA325580, NM_015064, gen.NM_015064
Figure 3431: PRO82078
Figure 3432: DNA325581, NM_030775, gen.NM_030775
Figure 3433: PRO71031
Figure 3434: DNA297398, NM_032642, gen.NM_032642
Figure 3435: PRO71031
Figure 3436: DNA325582, XM_017080, gen.XM_017080
Figure 3437: DNA325583, XM_113739, gen.XM_113739
Figure 3438: PRO82080
Figure 3439: DNA325584, NM_002014,

gen.NM_002014
 Figure 3440: PRO59262
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 Figure 3443: PRO82082
 Figure 3444: DNA325587, NM_021953, gen.NM_021953
 Figure 3445: PRO82083
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 Figure 3447: PRO82084
 Figure 3448: DNA325589, NM_005002, gen.NM_005002
 Figure 3449: PRO82085
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 Figure 3451: DNA325591, XM_116926, gen.XM_116926
 Figure 3452: DNA88114, NM_001734, gen.NM_001734
 Figure 3453: PRO2660
 Figure 3454: DNA325592, XM_058574, gen.XM_058574
 Figure 3455: DNA325593, NM_007273, gen.NM_007273
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 Figure 3457A-B: DNA325594, XM_032588, gen.XM_032588
 Figure 3458: DNA325595, NM_001975, gen.NM_001975
 Figure 3459: PRO38010
 Figure 3460: DNA325596, NM_000365, gen.NM_000365
 Figure 3461: PRO69549
 Figure 3462: DNA325597, XM_032614, gen.XM_032614
 Figure 3463: DNA325598, NM_002075, gen.NM_002075
 Figure 3464: PRO82091
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 Figure 3466: DNA151827, NM_005439, gen.NM_005439
 Figure 3467: PRO12902
 Figure 3468A-B: DNA254624, NM_001273, gen.NM_001273
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 Figure 3473: DNA225632, NM_002046, gen.NM_002046

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 Figure 3480: DNA188396, NM_001065, gen.NM_001065
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 Figure 3485A-B: DNA325605, XM_006925, gen.XM_006925
 Figure 3486: DNA325606, XM_096630, gen.XM_096630
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 Figure 3488: DNA325607, XM_084901, gen.XM_084901
 Figure 3489: DNA226028, NM_002355, gen.NM_002355
 Figure 3490: PRO36491
 Figure 3491: DNA325608, XM_031807, gen.XM_031807
 Figure 3492: PRO82101
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 Figure 3494: DNA325610, XM_012159, gen.XM_012159
 Figure 3495: DNA325611, XM_084922, gen.XM_084922
 Figure 3496: DNA325612, NM_031289, gen.NM_031289
 Figure 3497: PRO82104
 Figure 3498: DNA226771, NM_003979, gen.NM_003979
 Figure 3499: PRO37234
 Figure 3500: DNA325613, XM_084918, gen.XM_084918
 Figure 3501: DNA325614, NM_007178, gen.NM_007178
 Figure 3502: PRO82106
 Figure 3503: DNA325615, XM_041100, gen.XM_041100
 Figure 3504A-B: DNA325616, XM_058567, gen.XM_058567
 Figure 3505: PRO82107
 Figure 3506A-B: DNA325617, XM_166605, gen.XM_166605
 Figure 3507: DNA325618, XM_029805, gen.XM_029805

Figure 3508: PRO82109
Figure 3509: DNA325619, NM_005889, gen.NM_005889
Figure 3510: PRO82110
Figure 3511: DNA256072, NM_001644, gen.NM_001644
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Figure 3513: DNA325620, NM_018686, gen.NM_018686
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Figure 3520: DNA150978, NM_007244, gen.NM_007244
Figure 3521: PRO11601
Figure 3522: DNA325624, NM_006250, gen.NM_006250
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Figure 3524: DNA79313, NM_005042, gen.NM_005042
Figure 3525: PRO2555
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Figure 3528: DNA325625, XM_050074, gen.XM_050074
Figure 3529: DNA325626, NM_024854, gen.NM_024854
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Figure 3532: DNA325628, XM_165906, gen.XM_165906
Figure 3533A-B: DNA325629, XM_038659, gen.XM_038659
Figure 3534: PRO82120
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Figure 3536: DNA325631, XM_006748, gen.XM_006748
Figure 3537: PRO82122
Figure 3538: DNA325632, XM_016640, gen.XM_016640
Figure 3539: DNA325633, XM_096146, gen.XM_096146
Figure 3540A-B: DNA325634, XM_084841, gen.XM_084841
Figure 3541: PRO82125
Figure 3542: DNA325635, XM_090218, gen.XM_090218
Figure 3543: DNA325636, XM_012272, gen.XM_012272
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Figure 3546: DNA325638, NM_006262, gen.NM_006262
Figure 3547: PRO82129
Figure 3548: DNA325639, NM_018113, gen.NM_018113
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Figure 3555: DNA272379, NM_002733, gen.NM_002733
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Figure 3559: DNA325643, XM_006826, gen.XM_006826
Figure 3560: DNA325644, XM_113719, gen.XM_113719
Figure 3561: DNA325645, XM_028662, gen.XM_028662
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Figure 3572A-B: DNA325652, NM_016357, gen.NM_016357
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Figure 3579: DNA325656, XM_165905, gen.XM_165905
Figure 3580: DNA325657, XM_015481, gen.XM_015481
Figure 3581: DNA325658, XM_049148, gen.XM_049148
Figure 3582: DNA325659, XM_084885, gen.XM_084885
Figure 3583: DNA325660, XM_084884, gen.XM_084884
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Figure 3600: DNA196351, NM_002178, gen.NM_002178
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Figure 3604: DNA325670, NM_015665, gen.NM_015665
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Figure 3609: PRO82161
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Figure 3626: DNA325680, XM_006710, gen.XM_006710
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Figure 3631: DNA304783, NM_014255, gen.NM_014255
Figure 3632: PRO4426
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Figure 3635: DNA325684, XM_113712, gen.XM_113712
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Figure 3637: PRO82174
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Figure 3641: DNA325688, XM_053164, gen.XM_053164
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Figure 3653: PRO82184
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Figure 3661: PRO2846
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Figure 3681: DNA325710, NM_005981, gen.NM_005981
Figure 3682: PRO4666
Figure 3683: DNA325711, NM_000075, gen.NM_000075
Figure 3684: PRO4873
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Figure 3696: PRO82198
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Figure 3698: PRO82199
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Figure 3700: DNA325720, XM_056681, gen.XM_056681
Figure 3701: PRO82201
Figure 3702: DNA325721, XM_084909, gen.XM_084909
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Figure 3705: DNA325723, XM_084912, gen.XM_084912
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 Figure 3718: PRO71120
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 Figure 3720: DNA227474, NM_015646, gen.NM_015646
 Figure 3721: PRO37937
 Figure 3722: DNA325731, XM_053952, gen.XM_053952
 Figure 3723: PRO82212
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 Figure 3725: PRO37634
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 Figure 3727: DNA271492, NM_006530, gen.NM_006530
 Figure 3728: PRO59785
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 Figure 3735: PRO82214
 Figure 3736A-B: DNA325737, XM_006578, gen.XM_006578
 Figure 3737: DNA325738, XM_038308, gen.XM_038308
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 Figure 3739: DNA325739, XM_096597, gen.XM_096597
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 Figure 3751: PRO82221
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 Figure 3756: PRO82223
 Figure 3757: DNA325749, NM_003877, gen.NM_003877
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 Figure 3763: DNA274361, NM_000895, gen.NM_000895
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 Figure 3776: PRO82232
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 Figure 3781: DNA325762, NM_000970, gen.NM_000970
 Figure 3782: PRO82234
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Figure 3788A-B: DNA325766, XM_084941, gen.XM_084941
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Figure 3830: PRO70989
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Figure 3870: DNA325812, XM_084982, gen.XM_084982
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Figure 3927: PRO82305
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Figure 3956: PRO82322
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 gen.XM_016713
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 Figure 4181: PRO82434
 Figure 4182: DNA219233, NM_014335,
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 Figure 4183: PRO34557
 Figure 4184A-C: DNA325993, XM_034890,
 gen.XM_034890
 Figure 4185: PRO82435
 Figure 4186: DNA325994, XM_058684,
 gen.XM_058684
 Figure 4187: DNA325995, NM_003104,
 gen.NM_003104
 Figure 4188: PRO82437
 Figure 4189: DNA325996, XM_007651,
 gen.XM_007651
 Figure 4190: PRO82438
 Figure 4191: DNA325997, XM_090991,
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 Figure 4192: PRO82439
 Figure 4193: DNA325998, NM_016304,
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 Figure 4194: PRO82440
 Figure 4195: DNA325999, NM_017610,
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 Figure 4196: PRO82441
 Figure 4197: DNA326000, NM_004701,
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 Figure 4198: PRO82442
 Figure 4199A-B: DNA326001, XM_012418,
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 Figure 4200: DNA326002, XM_039702,
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 Figure 4202: DNA326003, XM_113266,
 gen.XM_113266

Figure 4203: DNA326004, NM_001218, gen.NM_001218
Figure 4204: PRO54594
Figure 4205: DNA326005, NM_015920, gen.NM_015920
Figure 4206: PRO82446
Figure 4207: DNA326006, XM_113268, gen.XM_113268
Figure 4208: DNA255340, NM_017684, gen.NM_017684
Figure 4209: PRO50409
Figure 4210: DNA326007, NM_002537, gen.NM_002537
Figure 4211: DNA326008, XM_085283, gen.XM_085283
Figure 4212: PRO82448
Figure 4213: DNA326009, XM_016985, gen.XM_016985
Figure 4214: DNA234442, NM_014736, gen.NM_014736
Figure 4215: PRO38852
Figure 4216: DNA326010, NM_022048, gen.NM_022048
Figure 4217: PRO82450
Figure 4218: DNA326011, NM_000942, gen.NM_000942
Figure 4219: PRO2720
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Figure 4221: DNA326013, XM_007623, gen.XM_007623
Figure 4222A-B: DNA326014, NM_133375, gen.NM_133375
Figure 4223: PRO82453
Figure 4224: DNA226646, NM_017882, gen.NM_017882
Figure 4225: PRO37109
Figure 4226: DNA326015, NM_015322, gen.NM_015322
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Figure 4228: DNA326016, NM_001003, gen.NM_001003
Figure 4229: PRO82455
Figure 4230A-B: DNA326017, XM_051463, gen.XM_051463
Figure 4231: PRO82456
Figure 4232: DNA326018, NM_018357, gen.NM_018357
Figure 4233: PRO82457
Figure 4234: DNA326019, XM_063639, gen.XM_063639
Figure 4235: PRO82458
Figure 4236: DNA326020, XM_085249, gen.XM_085249
Figure 4237: DNA326021, XM_016076, gen.XM_016076
Figure 4238: PRO82460
Figure 4239: DNA326022, XM_015366, gen.XM_015366
Figure 4240: PRO82461
Figure 4241: DNA326023, XM_096060, gen.XM_096060
Figure 4242: DNA287331, NM_002654, gen.NM_002654
Figure 4243: PRO69595
Figure 4244: DNA326024, XM_037778, gen.XM_037778
Figure 4245: DNA326025, XM_096842, gen.XM_096842
Figure 4246: DNA326026, NM_022369, gen.NM_022369
Figure 4247: PRO82465
Figure 4248: DNA326027, NM_032907, gen.NM_032907
Figure 4249: PRO82466
Figure 4250: DNA326028, XM_058699, gen.XM_058699
Figure 4251: DNA326029, XM_118637, gen.XM_118637
Figure 4252: DNA326030, XM_053585, gen.XM_053585
Figure 4253: PRO82469
Figure 4254: DNA326031, XM_085239, gen.XM_085239
Figure 4255: PRO82470
Figure 4256: DNA326032, XM_034897, gen.XM_034897
Figure 4257A-B: DNA326033, XM_057020, gen.XM_057020
Figure 4258: PRO82472
Figure 4259: DNA326034, NM_000743, gen.NM_000743
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Figure 4261: DNA326035, NM_002789, gen.NM_002789
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Figure 4263: DNA326036, XM_091100, gen.XM_091100
Figure 4264: PRO82473
Figure 4265: DNA255370, NM_012170, gen.NM_012170
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Figure 4268: PRO61085
Figure 4269: DNA326037, XM_044565, gen.XM_044565
Figure 4270: DNA326038, NM_025234, gen.NM_025234
Figure 4271: PRO82475
Figure 4272: DNA326039, XM_044569, gen.XM_044569

Figure 4273: DNA326040, NM_005724, gen.NM_005724
Figure 4274: PRO730
Figure 4275: DNA326041, XM_049354, gen.XM_049354
Figure 4276: PRO82477
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Figure 4278: DNA326043, XM_044593, gen.XM_044593
Figure 4279: DNA326044, NM_006791, gen.NM_006791
Figure 4280: PRO82479
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Figure 4283: DNA326047, NM_001021, gen.NM_001021
Figure 4284: PRO82482
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Figure 4286: DNA326049, XM_096844, gen.XM_096844
Figure 4287: DNA326050, XM_045681, gen.XM_045681
Figure 4288: PRO82485
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Figure 4294: PRO82489
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Figure 4296: DNA326056, NM_022566, gen.NM_022566
Figure 4297: PRO82491
Figure 4298A-B: DNA326057, XM_051860, gen.XM_051860
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Figure 4301: PRO62852
Figure 4302: DNA326058, NM_016645, gen.NM_016645
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Figure 4305: DNA150485, NM_006384, gen.NM_006384
Figure 4306: PRO12774

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Figure 4311A-B: DNA326063, XM_015835, gen.XM_015835
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Figure 4313: PRO82499
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Figure 4315: DNA326066, NM_033544, gen.NM_033544
Figure 4316: PRO82501
Figure 4317: DNA326067, XM_049372, gen.XM_049372
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Figure 4320: DNA275181, NM_003090, gen.NM_003090
Figure 4321: PRO62882
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Figure 4324: PRO82505
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Figure 4327: DNA326073, NM_017668, gen.NM_017668
Figure 4328: PRO82508
Figure 4329: DNA326074, XM_027309, gen.XM_027309
Figure 4330: PRO82509
Figure 4331: DNA326075, XM_018432, gen.XM_018432
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Figure 4333: DNA326076, XM_115352, gen.XM_115352
Figure 4334: DNA326077, XM_027365, gen.XM_027365
Figure 4335: DNA326078, NM_016641, gen.NM_016641
Figure 4336: PRO38464
Figure 4337: DNA326079, XM_058796, gen.XM_058796
Figure 4338: DNA326080, XM_017984, gen.XM_017984
Figure 4339: PRO82513
Figure 4340: DNA326081, NM_020677,

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Figure 4342: DNA326082, XM_036680, gen.XM_036680
Figure 4343: PRO37961
Figure 4344A-B: DNA326083, XM_048119, gen.XM_048119
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Figure 4347: PRO82516
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Figure 4349: PRO82517
Figure 4350: DNA326086, NM_024571, gen.NM_024571
Figure 4351: PRO82518
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Figure 4353: DNA326088, XM_008126, gen.XM_008126
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Figure 4355: PRO3629
Figure 4356: DNA326090, NM_000558, gen.NM_000558
Figure 4357: PRO3629
Figure 4358: DNA326091, NM_018032, gen.NM_018032
Figure 4359: PRO38311
Figure 4360: DNA273839, NM_006428, gen.NM_006428
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Figure 4362A-B: DNA256844, NM_005632, gen.NM_005632
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Figure 4364: DNA326092, XM_083939, gen.XM_083939
Figure 4365: PRO82521
Figure 4366: DNA326093, NM_058192, gen.NM_058192
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Figure 4368: DNA326094, XM_027412, gen.XM_027412
Figure 4369: PRO82523
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Figure 4375: PRO49879
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Figure 4379: PRO82525
Figure 4380: DNA326098, XM_034590, gen.XM_034590
Figure 4381: PRO82526
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Figure 4385: PRO82528
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Figure 4389: PRO82530
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Figure 4391: PRO82531
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Figure 4393: PRO82532
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Figure 4395: PRO82533
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Figure 4399: PRO12683
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Figure 4416: DNA326117, NM_002484, gen.NM_002484
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Figure 4419: PRO82544
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Figure 4431: DNA326126, XM_113874, gen.XM_113874
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Figure 4433: PRO82551
Figure 4434: DNA326128, XM_086278, gen.XM_086278
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Figure 4438A-B: DNA326131, XM_056260, gen.XM_056260
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Figure 4468: DNA326148, NM_022744, gen.NM_022744
Figure 4469: PRO82570
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Figure 4471: PRO82571
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Figure 4537: DNA326183, XM_165648, gen.XM_165648
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 Figure 4644A-B: DNA326240, XM_017096, gen.XM_017096
 Figure 4645: DNA326241, XM_033714, gen.XM_033714
 Figure 4646A-B: DNA326242, XM_033689, gen.XM_033689
 Figure 4647: DNA326243, NM_002615, gen.NM_002615
 Figure 4648: DNA326244, XM_056082, gen.XM_056082
 Figure 4649: PRO82654
 Figure 4650: DNA326245, XM_008557, gen.XM_008557
 Figure 4651: DNA326246, XM_045183, gen.XM_045183
 Figure 4652: PRO82656
 Figure 4653: DNA326247, XM_113901, gen.XM_113901
 Figure 4654: DNA326248, NM_080822, gen.NM_080822
 Figure 4655: PRO82658
 Figure 4656A-B: DNA326249, XM_029438, gen.XM_029438
 Figure 4657: PRO82659
 Figure 4658: DNA326250, XM_008509,

gen.XM_008509
 Figure 4659: DNA326251, XM_085687, gen.XM_085687
 Figure 4660: PRO82661
 Figure 4661: DNA326252, XM_027825, gen.XM_027825
 Figure 4662: PRO82662
 Figure 4663: DNA326253, XM_053717, gen.XM_053717
 Figure 4664: PRO82663
 Figure 4665: DNA326254, NM_005022, gen.NM_005022
 Figure 4666: PRO62780
 Figure 4667A-B: DNA326255, XM_028398, gen.XM_028398
 Figure 4668: PRO82664
 Figure 4669: DNA326256, NM_000018, gen.NM_000018
 Figure 4670: PRO66265
 Figure 4671: DNA326257, XM_008334, gen.XM_008334
 Figure 4672: DNA326258, NM_024297, gen.NM_024297
 Figure 4673: PRO82665
 Figure 4674: DNA326259, XM_113324, gen.XM_113324
 Figure 4675: DNA326260, XM_012676, gen.XM_012676
 Figure 4676: PRO82667
 Figure 4677: DNA326261, XM_085691, gen.XM_085691
 Figure 4678: DNA326262, XM_028417, gen.XM_028417
 Figure 4679: PRO82669
 Figure 4680A-B: DNA326263, XM_041964, gen.XM_041964
 Figure 4681: PRO82670
 Figure 4682: DNA326264, NM_019013, gen.NM_019013
 Figure 4683: PRO82671
 Figure 4684: DNA326265, XM_008538, gen.XM_008538
 Figure 4685: PRO82672
 Figure 4686: DNA326266, XM_008441, gen.XM_008441
 Figure 4687: DNA97300, NM_001416, gen.NM_001416
 Figure 4688: PRO3647
 Figure 4689: DNA326267, NM_004870, gen.NM_004870
 Figure 4690: PRO82674
 Figure 4691: DNA326268, NM_006942, gen.NM_006942
 Figure 4692: PRO82675
 Figure 4693: DNA326269, XM_008679, gen.XM_008679

Figure 4694: DNA326270, XM_008231, gen.XM_008231
Figure 4695: DNA326271, XM_113328, gen.XM_113328
Figure 4696: DNA326272, XM_113929, gen.XM_113929
Figure 4697: DNA326273, NM_001970, gen.NM_001970
Figure 4698: PRO82678
Figure 4699: DNA297388, NM_004217, gen.NM_004217
Figure 4700: PRO70812
Figure 4701: DNA326274, XM_165421, gen.XM_165421
Figure 4702: PRO82679
Figure 4703: DNA326275, XM_113325, gen.XM_113325
Figure 4704: DNA326276, XM_165422, gen.XM_165422
Figure 4705: PRO49182
Figure 4706: DNA326277, XM_113931, gen.XM_113931
Figure 4707: DNA326278, XM_036659, gen.XM_036659
Figure 4708: DNA103401, NM_003876, gen.NM_003876
Figure 4709: PRO4729
Figure 4710A-B: DNA326279, XM_042698, gen.XM_042698
Figure 4711: PRO82683
Figure 4712A-B: DNA326280, XM_017234, gen.XM_017234
Figure 4713: DNA326281, XM_165418, gen.XM_165418
Figure 4714: DNA304715, NM_000987, gen.NM_000987
Figure 4715: PRO711141
Figure 4716A-B: DNA326282, NM_004618, gen.NM_004618
Figure 4717: PRO62981
Figure 4718: DNA326283, XM_085743, gen.XM_085743
Figure 4719A-B: DNA254198, NM_002018, gen.NM_002018
Figure 4720: PRO49310
Figure 4721A-B: DNA326284, XM_039910, gen.XM_039910
Figure 4722: PRO82687
Figure 4723A-C: DNA326285, XM_113310, gen.XM_113310
Figure 4724: DNA326286, XM_085613, gen.XM_085613
Figure 4725: DNA326287, NM_006470, gen.NM_006470
Figure 4726: PRO82689
Figure 4727: DNA326288, XM_051763, gen.XM_051763
Figure 4728: DNA290292, NM_018955, gen.NM_018955
Figure 4729: PRO70449
Figure 4730: DNA326289, XM_058900, gen.XM_058900
Figure 4731: PRO82691
Figure 4732: DNA326290, XM_039921, gen.XM_039921
Figure 4733: PRO82692
Figure 4734: DNA326291, XM_012549, gen.XM_012549
Figure 4735: DNA326292, XM_085548, gen.XM_085548
Figure 4736: PRO82694
Figure 4737: DNA326293, NM_018019, gen.NM_018019
Figure 4738: PRO82695
Figure 4739: DNA326294, NM_138427, gen.NM_138427
Figure 4740: PRO82696
Figure 4741: DNA326295, XM_085545, gen.XM_085545
Figure 4742A-B: DNA227084, NM_004176, gen.NM_004176
Figure 4743: PRO37547
Figure 4744: DNA326296, XM_012615, gen.XM_012615
Figure 4745: DNA326297, XM_085722, gen.XM_085722
Figure 4746: PRO82699
Figure 4747: DNA255414, NM_018242, gen.NM_018242
Figure 4748: PRO50481
Figure 4749: DNA326298, XM_045044, gen.XM_045044
Figure 4750: DNA326299, XM_008323, gen.XM_008323
Figure 4751: DNA326300, XM_045535, gen.XM_045535
Figure 4752A-B: DNA326301, XM_045551, gen.XM_045551
Figure 4753: PRO82702
Figure 4754: DNA326302, XM_097204, gen.XM_097204
Figure 4755: DNA326303, XM_058867, gen.XM_058867
Figure 4756: PRO82704
Figure 4757: DNA326304, XM_085672, gen.XM_085672
Figure 4758: DNA326305, XM_031536, gen.XM_031536
Figure 4759: PRO82706
Figure 4760: DNA326306, XM_008486, gen.XM_008486
Figure 4761: DNA326307, NM_015584,

gen.NM_015584
 Figure 4762: PRO82707
 Figure 4763: DNA326308, NM_000638,
 gen.NM_000638
 Figure 4764: PRO82708
 Figure 4765A-B: DNA326309, XM_031466,
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 Figure 4766: PRO82709
 Figure 4767: DNA326310, XM_031415,
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 Figure 4768: DNA326311, XM_117066,
 gen.XM_117066
 Figure 4769: DNA326312, XM_031427,
 gen.XM_031427
 Figure 4770: PRO82712
 Figure 4771: DNA326313, NM_032322,
 gen.NM_032322
 Figure 4772: PRO82713
 Figure 4773A-B: DNA326314, XM_050101,
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 Figure 4774: PRO82714
 Figure 4775: DNA326315, XM_056730,
 gen.XM_056730
 Figure 4776: PRO82715
 Figure 4777: DNA326316, XM_008462,
 gen.XM_008462
 Figure 4778: DNA287427, NM_002815,
 gen.NM_002815
 Figure 4779: PRO69684
 Figure 4780: DNA326317, NM_015544,
 gen.NM_015544
 Figure 4781: PRO82717
 Figure 4782: DNA188351, NM_005623,
 gen.NM_005623
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 Figure 4784: DNA326318, NM_002878,
 gen.NM_002878
 Figure 4785: PRO82718
 Figure 4786: DNA326319, NM_133627,
 gen.NM_133627
 Figure 4787: PRO82719
 Figure 4788: DNA326320, NM_133630,
 gen.NM_133630
 Figure 4789: PRO82720
 Figure 4790: DNA326321, NM_133629,
 gen.NM_133629
 Figure 4791: PRO82721
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 Figure 4793: PRO37791
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 Figure 4795: PRO82722
 Figure 4796A-B: DNA66475, NM_004448,
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 Figure 4797: PRO1204

Figure 4798: DNA326324, NM_000981,
 gen.NM_000981
 Figure 4799: PRO4738
 Figure 4800A-B: DNA326325, XM_008150,
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 Figure 4801: DNA326326, NM_000978,
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 Figure 4802: PRO82724
 Figure 4803: DNA326327, XM_058830,
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 Figure 4804: PRO82725
 Figure 4805: DNA270979, NM_002809,
 gen.NM_002809
 Figure 4806: PRO59309
 Figure 4807: DNA326328, NM_000422,
 gen.NM_000422
 Figure 4808: PRO82726
 Figure 4809: DNA326329, XM_008579,
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 Figure 4810: DNA326330, NM_002276,
 gen.NM_002276
 Figure 4811: PRO82728
 Figure 4812: DNA272889, NM_002275,
 gen.NM_002275
 Figure 4813: PRO60979
 Figure 4814: DNA326331, NM_002274,
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 Figure 4815: PRO82729
 Figure 4816: DNA326332, NM_000526,
 gen.NM_000526
 Figure 4817: PRO82730
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 gen.XM_049937
 Figure 4819A-B: DNA326334, XM_113334,
 gen.XM_113334
 Figure 4820: DNA226389, NM_000964,
 gen.NM_000964
 Figure 4821: PRO36852
 Figure 4822: DNA326335, NM_006455,
 gen.NM_006455
 Figure 4823: PRO82732
 Figure 4824: DNA326336, XM_113938,
 gen.XM_113938
 Figure 4825: DNA326337, XM_036465,
 gen.XM_036465
 Figure 4826: DNA326338, XM_055061,
 gen.XM_055061
 Figure 4827A-B: DNA326339, XM_036462,
 gen.XM_036462
 Figure 4828: PRO82736
 Figure 4829: DNA326340, XM_048654,
 gen.XM_048654
 Figure 4830: DNA326341, NM_025197,
 gen.NM_025197
 Figure 4831: PRO82737
 Figure 4832: DNA326342, XM_054038,

gen.XM_054038
Figure 4833: PRO82738
Figure 4834: DNA326343, NM_002265, gen.NM_002265
Figure 4835: PRO82739
Figure 4836: DNA326344, XM_032201, gen.XM_032201
Figure 4837: PRO82740
Figure 4838: DNA326345, NM_012138, gen.NM_012138
Figure 4839: PRO82741
Figure 4840: DNA326346, XM_018534, gen.XM_018534
Figure 4841: DNA227873, NM_001050, gen.NM_001050
Figure 4842: PRO38336
Figure 4843: DNA270975, NM_000386, gen.NM_000386
Figure 4844: PRO59305
Figure 4845: DNA88378, NM_002087, gen.NM_002087
Figure 4846: PRO2769
Figure 4847: DNA326347, NM_016016, gen.NM_016016
Figure 4848: PRO82743
Figure 4849: DNA326348, XM_012642, gen.XM_012642
Figure 4850A-B: DNA326349, NM_005474, gen.NM_005474
Figure 4851: PRO82745
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Figure 4853: PRO82746
Figure 4854: DNA257428, NM_032376, gen.NM_032376
Figure 4855: PRO52010
Figure 4856: DNA326351, XM_008351, gen.XM_008351
Figure 4857: DNA326352, XM_032852, gen.XM_032852
Figure 4858: PRO82748
Figure 4859: DNA326353, NM_025233, gen.NM_025233
Figure 4860: PRO82749
Figure 4861: DNA326354, XM_032817, gen.XM_032817
Figure 4862: PRO82750
Figure 4863: DNA326355, XM_032813, gen.XM_032813
Figure 4864: DNA326356, XM_032766, gen.XM_032766
Figure 4865: DNA326357, NM_003766, gen.NM_003766
Figure 4866: PRO82753
Figure 4867: DNA326358, XM_008401, gen.XM_008401

Figure 4868: PRO82754
Figure 4869: DNA326359, XM_008402, gen.XM_008402
Figure 4870: PRO82755
Figure 4871: DNA326360, NM_017595, gen.NM_017595
Figure 4872: PRO82756
Figure 4873: DNA326361, XM_085636, gen.XM_085636
Figure 4874: PRO82757
Figure 4875: DNA326362, NM_006373, gen.NM_006373
Figure 4876: PRO82758
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Figure 4878: PRO25115
Figure 4879A-B: DNA270901, NM_004247, gen.NM_004247
Figure 4880: DNA326363, XM_050159, gen.XM_050159
Figure 4881: DNA326364, XM_083983, gen.XM_083983
Figure 4882: PRO82760
Figure 4883A-B: DNA326365, NM_021079, gen.NM_021079
Figure 4884: PRO82761
Figure 4885: DNA326366, NM_133373, gen.NM_133373
Figure 4886: PRO82762
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Figure 4888: PRO3637
Figure 4889: DNA227071, NM_000269, gen.NM_000269
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Figure 4891: DNA227764, NM_003971, gen.NM_003971
Figure 4892: PRO38227
Figure 4893A-B: DNA326367, NM_020038, gen.NM_020038
Figure 4894: PRO82763
Figure 4895A-B: DNA326368, NM_020037, gen.NM_020037
Figure 4896: PRO82764
Figure 4897: DNA326369, XM_037971, gen.XM_037971
Figure 4898: DNA254791, NM_018346, gen.NM_018346
Figure 4899: PRO49888
Figure 4900: DNA287425, NM_018509, gen.NM_018509
Figure 4901: PRO69682
Figure 4902A-B: DNA326370, XM_008432, gen.XM_008432
Figure 4903: DNA88554, NM_000250, gen.NM_000250

Figure 4904: PRO2839
 Figure 4905: DNA326371, XM_113919, gen.XM_113919
 Figure 4906: DNA326372, NM_017777, gen.NM_017777
 Figure 4907: PRO82768
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 Figure 4909: PRO82769
 Figure 4910: DNA326374, XM_115480, gen.XM_115480
 Figure 4911: DNA326375, NM_005831, gen.NM_005831
 Figure 4912: PRO59328
 Figure 4913: DNA326376, XM_117061, gen.XM_117061
 Figure 4914: PRO82771
 Figure 4915: DNA326377, XM_008459, gen.XM_008459
 Figure 4916A-B: DNA326378, XM_012651, gen.XM_012651
 Figure 4917: DNA326379, NM_021626, gen.NM_021626
 Figure 4918: PRO302
 Figure 4919: DNA287291, NM_021213, gen.NM_021213
 Figure 4920: PRO69561
 Figure 4921A-B: DNA326380, NM_004859, gen.NM_004859
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 Figure 4923: DNA326381, XM_083966, gen.XM_083966
 Figure 4924: DNA326382, XM_044426, gen.XM_044426
 Figure 4925: PRO82776
 Figure 4926: DNA326383, XM_008253, gen.XM_008253
 Figure 4927: DNA326384, XM_044394, gen.XM_044394
 Figure 4928: PRO10400
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 Figure 4930: PRO82778
 Figure 4931: DNA326386, NM_007372, gen.NM_007372
 Figure 4932: PRO82779
 Figure 4933: DNA326387, NM_002401, gen.NM_002401
 Figure 4934: PRO37764
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 Figure 4936A-B: DNA150457, NM_006039, gen.NM_006039
 Figure 4937: PRO12265
 Figure 4938: DNA326389, XM_044367, gen.XM_044367

Figure 4939: DNA227055, NM_002634, gen.NM_002634
 Figure 4940: PRO37518
 Figure 4941: DNA326390, XM_011118, gen.XM_011118
 Figure 4942: DNA326391, XM_055199, gen.XM_055199
 Figure 4943A-B: DNA326392, XM_044372, gen.XM_044372
 Figure 4944: DNA326393, XM_113315, gen.XM_113315
 Figure 4945: DNA326394, XM_012609, gen.XM_012609
 Figure 4946: DNA326395, NM_005220, gen.NM_005220
 Figure 4947: PRO82787
 Figure 4948: DNA326396, XM_085589, gen.XM_085589
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 Figure 4952: PRO82790
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 Figure 4954: PRO12806
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 Figure 4958: DNA326401, XM_046932, gen.XM_046932
 Figure 4959: PRO82792
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 Figure 4965A-B: DNA326404, XM_036104, gen.XM_036104
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 Figure 4971A-B: DNA326407, XM_036115, gen.XM_036115
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 Figure 4974: PRO82797
 Figure 4975: DNA274755, NM_002766, gen.NM_002766
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 Figure 4985: DNA129504, NM_001168, gen.NM_001168
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 Figure 5002: DNA326426, NM_004309, gen.NM_004309
 Figure 5003: PRO61246
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 Figure 5005: PRO82812
 Figure 5006: DNA326428, NM_016286, gen.NM_016286

Figure 5007: PRO82813
 Figure 5008: DNA326429, NM_004127, gen.NM_004127
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 Figure 5020: DNA326436, XM_046765, gen.XM_046765
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 Figure 5024: PRO61661
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 Figure 5027: DNA326441, XM_041678, gen.XM_041678
 Figure 5028: DNA326442, XM_113343, gen.XM_113343
 Figure 5029: PRO82825
 Figure 5030: DNA326443, XM_067325, gen.XM_067325
 Figure 5031: DNA326444, XM_012741, gen.XM_012741
 Figure 5032: DNA326445, NM_014214, gen.NM_014214
 Figure 5033: PRO82828
 Figure 5034A-B: DNA326446, XM_035640, gen.XM_035640
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 Figure 5036: DNA326447, XM_016382, gen.XM_016382
 Figure 5037: DNA326448, NM_032933, gen.NM_032933
 Figure 5038: PRO82831
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Figure 5040A-B: DNA88457, NM_000227, gen.NM_000227
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Figure 5044: PRO82833
Figure 5045: DNA326451, XM_085790, gen.XM_085790
Figure 5046: DNA326452, XM_015755, gen.XM_015755
Figure 5047: PRO82835
Figure 5048: DNA326453, XM_097232, gen.XM_097232
Figure 5049: DNA326454, XM_085788, gen.XM_085788
Figure 5050: DNA88281, NM_001944, gen.NM_001944
Figure 5051: PRO2267
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Figure 5053: PRO60121
Figure 5054: DNA326455, XM_008723, gen.XM_008723
Figure 5055: DNA326456, XM_084007, gen.XM_084007
Figure 5056: DNA256813, NM_018255, gen.NM_018255
Figure 5057: PRO51744
Figure 5058: DNA326457, XM_085775, gen.XM_085775
Figure 5059: PRO82840
Figure 5060: DNA326458, NM_138443, gen.NM_138443
Figure 5061: PRO82841
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Figure 5063: PRO82842
Figure 5064: DNA326460, XM_086779, gen.XM_086779
Figure 5065: DNA326461, XM_167363, gen.XM_167363
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Figure 5067: DNA326463, NM_000985, gen.NM_000985
Figure 5068: PRO82846
Figure 5069: DNA326464, NM_002396, gen.NM_002396
Figure 5070: PRO61113
Figure 5071: DNA326465, XM_166288, gen.XM_166288
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Figure 5073: PRO60800

Figure 5074: DNA326467, XM_006937, gen.XM_006937
Figure 5075: DNA326468, XM_085779, gen.XM_085779
Figure 5076: DNA326469, XM_011089, gen.XM_011089
Figure 5077: PRO82850
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Figure 5083A-B: DNA326473, XM_008812, gen.XM_008812
Figure 5084A-B: DNA326474, XM_117096, gen.XM_117096
Figure 5085: PRO82855
Figure 5086: DNA326475, NM_002385, gen.NM_002385
Figure 5087: PRO82856
Figure 5088: DNA326476, XM_015241, gen.XM_015241
Figure 5089A-B: DNA326477, XM_008695, gen.XM_008695
Figure 5090A-B: DNA326478, XM_041872, gen.XM_041872
Figure 5091: PRO82859
Figure 5092: DNA326479, XM_051586, gen.XM_051586
Figure 5093: DNA326480, NM_003712, gen.NM_003712
Figure 5094: PRO1077
Figure 5095: DNA326481, XM_042018, gen.XM_042018
Figure 5096: PRO2560
Figure 5097: DNA326482, XM_114018, gen.XM_114018
Figure 5098: DNA326483, NM_017876, gen.NM_017876
Figure 5099: PRO82861
Figure 5100: DNA326484, NM_031990, gen.NM_031990
Figure 5101: PRO82862
Figure 5102: DNA326485, NM_002819, gen.NM_002819
Figure 5103: PRO62899
Figure 5104: DNA326486, NM_005224, gen.NM_005224
Figure 5105: PRO82863
Figure 5106: DNA326487, XM_037565, gen.XM_037565
Figure 5107: PRO82864
Figure 5108: DNA326488, XM_092042,

gen.XM_092042
Figure 5109: DNA326489, XM_037572, gen.XM_037572
Figure 5110: DNA326490, XM_009279, gen.XM_009279
Figure 5111: PRO82867
Figure 5112: DNA326491, NM_002085, gen.NM_002085
Figure 5113A-B: DNA326492, XM_009277, gen.XM_009277
Figure 5114: DNA326493, XM_012913, gen.XM_012913
Figure 5115: DNA274101, NM_001687, gen.NM_001687
Figure 5116: PRO62039
Figure 5117: DNA326494, XM_028067, gen.XM_028067
Figure 5118: PRO82871
Figure 5119: DNA326495, XM_028064, gen.XM_028064
Figure 5120: DNA326496, NM_024407, gen.NM_024407
Figure 5121: PRO82872
Figure 5122: DNA326497, NM_000156, gen.NM_000156
Figure 5123: PRO58046
Figure 5124: DNA326498, NM_138924, gen.NM_138924
Figure 5125: PRO82873
Figure 5126: DNA326499, NM_001018, gen.NM_001018
Figure 5127: PRO10485
Figure 5128: DNA326500, XM_086101, gen.XM_086101
Figure 5129: PRO82874
Figure 5130: DNA326501, XM_086102, gen.XM_086102
Figure 5131: DNA326502, XM_047584, gen.XM_047584
Figure 5132A-B: DNA326503, XM_047600, gen.XM_047600
Figure 5133: PRO38496
Figure 5134: DNA326504, XM_097420, gen.XM_097420
Figure 5135A-B: DNA326505, XM_030721, gen.XM_030721
Figure 5136: PRO82877
Figure 5137: DNA326506, XM_030720, gen.XM_030720
Figure 5138: DNA326507, NM_031213, gen.NM_031213
Figure 5139: PRO82879
Figure 5140: DNA326508, XM_039723, gen.XM_039723
Figure 5141: DNA326509, NM_001319, gen.NM_001319

Figure 5142: PRO82881
Figure 5143: DNA326510, NM_017797, gen.NM_017797
Figure 5144: PRO82882
Figure 5145: DNA326511, XM_030714, gen.XM_030714
Figure 5146: DNA256555, NM_017572, gen.NM_017572
Figure 5147: PRO51586
Figure 5148A-B: DNA326512, NM_003938, gen.NM_003938
Figure 5149: PRO82884
Figure 5150A-B: DNA326513, XM_046822, gen.XM_046822
Figure 5151: PRO82885
Figure 5152: DNA326514, NM_007165, gen.NM_007165
Figure 5153: PRO82886
Figure 5154: DNA287636, NM_004152, gen.NM_004152
Figure 5155: DNA326515, NM_012458, gen.NM_012458
Figure 5156: PRO82887
Figure 5157: DNA326516, NM_032737, gen.NM_032737
Figure 5158: PRO82888
Figure 5159: DNA326517, XM_030485, gen.XM_030485
Figure 5160: DNA326518, XM_046934, gen.XM_046934
Figure 5161: DNA326519, NM_003021, gen.NM_003021
Figure 5162: PRO62302
Figure 5163: DNA326520, XM_055686, gen.XM_055686
Figure 5164: PRO37951
Figure 5165: DNA326521, XM_009222, gen.XM_009222
Figure 5166: DNA326522, XM_052635, gen.XM_052635
Figure 5167: PRO82892
Figure 5168: DNA326523, XM_052661, gen.XM_052661
Figure 5169: DNA326524, NM_016263, gen.NM_016263
Figure 5170: PRO82893
Figure 5171: DNA326525, NM_006339, gen.NM_006339
Figure 5172: PRO82894
Figure 5173: DNA326526, NM_032753, gen.NM_032753
Figure 5174: PRO82895
Figure 5175: DNA326527, XM_056421, gen.XM_056421
Figure 5176A-B: DNA326528, XM_031917, gen.XM_031917

Figure 5177: PRO82897
Figure 5178: DNA326529, NM_001961, gen.NM_001961
Figure 5179: PRO62225
Figure 5180: DNA326530, XM_016871, gen.XM_016871
Figure 5181: DNA326531, NM_016539, gen.NM_016539
Figure 5182: PRO82899
Figure 5183: DNA326532, XM_117122, gen.XM_117122
Figure 5184: DNA326533, XM_031857, gen.XM_031857
Figure 5185: PRO82901
Figure 5186: DNA326534, NM_024333, gen.NM_024333
Figure 5187: PRO82902
Figure 5188: DNA326535, NM_003025, gen.NM_003025
Figure 5189: PRO82903
Figure 5190: DNA326536, NM_025241, gen.NM_025241
Figure 5191: PRO82904
Figure 5192: DNA326537, XM_035638, gen.XM_035638
Figure 5193: PRO82905
Figure 5194A-B: DNA326538, XM_035636, gen.XM_035636
Figure 5195: DNA326539, XM_012862, gen.XM_012862
Figure 5196A-B: DNA326540, XM_035627, gen.XM_035627
Figure 5197A-B: DNA326541, XM_035625, gen.XM_035625
Figure 5198: PRO82909
Figure 5199: DNA274761, NM_014649, gen.NM_014649
Figure 5200: PRO62531
Figure 5201: DNA272421, NM_006012, gen.NM_006012
Figure 5202: PRO60674
Figure 5203: DNA326542, NM_003685, gen.NM_003685
Figure 5204: PRO82910
Figure 5205A-B: DNA326543, XM_009010, gen.XM_009010
Figure 5206: DNA270315, NM_004240, gen.NM_004240
Figure 5207: PRO58702
Figure 5208: DNA326544, NM_005490, gen.NM_005490
Figure 5209: PRO201
Figure 5210: DNA326546, XM_044619, gen.XM_044619
Figure 5211: PRO82912
Figure 5212: DNA326547, XM_012798, gen.XM_012798
Figure 5213: DNA326548, XM_044608, gen.XM_044608
Figure 5214: DNA326549, NM_003624, gen.NM_003624
Figure 5215: PRO82915
Figure 5216: DNA326550, NM_016579, gen.NM_016579
Figure 5217: PRO224
Figure 5218A-B: DNA326551, XM_048351, gen.XM_048351
Figure 5219: DNA326552, XM_048364, gen.XM_048364
Figure 5220: PRO82917
Figure 5221: DNA326553, XM_091938, gen.XM_091938
Figure 5222: DNA326554, XM_097300, gen.XM_097300
Figure 5223: DNA326555, XM_049282, gen.XM_049282
Figure 5224: PRO82920
Figure 5225: DNA326556, XM_058232, gen.XM_058232
Figure 5226: DNA326557, XM_045151, gen.XM_045151
Figure 5227A-B: DNA326558, XM_050435, gen.XM_050435
Figure 5228: PRO82923
Figure 5229: DNA326559, XM_113988, gen.XM_113988
Figure 5230: DNA326560, NM_058164, gen.NM_058164
Figure 5231: PRO82925
Figure 5232: DNA227280, NM_020230, gen.NM_020230
Figure 5233: PRO37743
Figure 5234: DNA270621, NM_003755, gen.NM_003755
Figure 5235: PRO58991
Figure 5236: DNA326561, XM_049502, gen.XM_049502
Figure 5237: DNA326562, NM_007065, gen.NM_007065
Figure 5238: PRO63226
Figure 5239: DNA326563, XM_049561, gen.XM_049561
Figure 5240: DNA326564, XM_017204, gen.XM_017204
Figure 5241: DNA326565, NM_005498, gen.NM_005498
Figure 5242: PRO62112
Figure 5243: DNA326566, XM_008887, gen.XM_008887
Figure 5244: DNA326567, XM_085862, gen.XM_085862
Figure 5245: PRO82930

Figure 5246: DNA326568, XM_084014, gen.XM_084014
Figure 5247A-B: DNA326569, XM_032710, gen.XM_032710
Figure 5248: DNA326570, XM_032719, gen.XM_032719
Figure 5249: PRO82933
Figure 5250: DNA326571, NM_024029, gen.NM_024029
Figure 5251: PRO23794
Figure 5252: DNA326572, XM_032724, gen.XM_032724
Figure 5253: PRO82934
Figure 5254A-B: DNA326573, NM_003072, gen.NM_003072
Figure 5255: PRO82935
Figure 5256A-B: DNA326574, XM_009082, gen.XM_009082
Figure 5257: DNA326575, XM_032774, gen.XM_032774
Figure 5258: DNA218271, NM_000121, gen.NM_000121
Figure 5259: PRO34323
Figure 5260: DNA326576, XM_057074, gen.XM_057074
Figure 5261: DNA326577, XM_032782, gen.XM_032782
Figure 5262: DNA326578, NM_032377, gen.NM_032377
Figure 5263: PRO82939
Figure 5264: DNA326579, XM_015697, gen.XM_015697
Figure 5265: PRO82940
Figure 5266: DNA326580, XM_010156, gen.XM_010156
Figure 5267: DNA326581, NM_001930, gen.NM_001930
Figure 5268: PRO58446
Figure 5269: DNA326582, NM_013406, gen.NM_013406
Figure 5270: DNA326583, NM_013407, gen.NM_013407
Figure 5271: PRO82943
Figure 5272: DNA103320, NM_002229, gen.NM_002229
Figure 5273: PRO4650
Figure 5274: DNA326584, XM_009063, gen.XM_009063
Figure 5275: PRO82944
Figure 5276: DNA326585, XM_085917, gen.XM_085917
Figure 5277: DNA274034, NM_006397, gen.NM_006397
Figure 5278: PRO61977
Figure 5279: DNA287243, NM_004461, gen.NM_004461
Figure 5280: PRO69518
Figure 5281: DNA326586, XM_032020, gen.XM_032020
Figure 5282: PRO2718
Figure 5283: DNA326587, NM_005053, gen.NM_005053
Figure 5284: PRO22613
Figure 5285: DNA326588, XM_085916, gen.XM_085916
Figure 5286: DNA326589, NM_017722, gen.NM_017722
Figure 5287: PRO82947
Figure 5288: DNA326590, NM_003765, gen.NM_003765
Figure 5289: PRO82948
Figure 5290: DNA326591, XM_051364, gen.XM_051364
Figure 5291: PRO82949
Figure 5292: DNA326592, XM_031345, gen.XM_031345
Figure 5293: PRO82950
Figure 5294: DNA326593, XM_113352, gen.XM_113352
Figure 5295: DNA326594, XM_058967, gen.XM_058967
Figure 5296: PRO82952
Figure 5297: DNA326595, XM_085909, gen.XM_085909
Figure 5298: DNA269894, NM_002730, gen.NM_002730
Figure 5299: PRO58292
Figure 5300: DNA326596, NM_018154, gen.NM_018154
Figure 5301: PRO82954
Figure 5302: DNA326597, XM_031276, gen.XM_031276
Figure 5303: DNA326598, XM_031273, gen.XM_031273
Figure 5304: PRO82956
Figure 5305: DNA326599, XM_031263, gen.XM_031263
Figure 5306: PRO82957
Figure 5307: DNA326600, XM_031251, gen.XM_031251
Figure 5308: DNA326601, NM_006844, gen.NM_006844
Figure 5309: PRO82958
Figure 5310A-C: DNA326602, XM_009303, gen.XM_009303
Figure 5311: DNA326603, XM_086074, gen.XM_086074
Figure 5312: DNA269630, NM_003290, gen.NM_003290
Figure 5313: PRO58042
Figure 5314: DNA326604, NM_005370, gen.NM_005370

Figure 5315: PRO12130
Figure 5316: DNA326605, XM_113348, gen.XM_113348
Figure 5317: DNA326606, NM_032207, gen.NM_032207
Figure 5318: PRO82962
Figure 5319A-B: DNA326607, NM_006387, gen.NM_006387
Figure 5320: PRO82963
Figure 5321: DNA326608, NM_024881, gen.NM_024881
Figure 5322: PRO82964
Figure 5323: DNA326609, NM_024104, gen.NM_024104
Figure 5324: PRO82965
Figure 5325A-C: DNA326610, XM_008854, gen.XM_008854
Figure 5326: DNA326611, NM_014173, gen.NM_014173
Figure 5327: PRO82967
Figure 5328: DNA287240, NM_004335, gen.NM_004335
Figure 5329: PRO29371
Figure 5330: DNA326612, XM_050660, gen.XM_050660
Figure 5331: DNA326613, XM_086116, gen.XM_086116
Figure 5332: DNA326614, NM_018174, gen.NM_018174
Figure 5333: PRO82970
Figure 5334: DNA326615, NM_000980, gen.NM_000980
Figure 5335: PRO82971
Figure 5336: DNA326616, XM_055230, gen.XM_055230
Figure 5337: DNA326617, XM_012179, gen.XM_012179
Figure 5338A-B: DNA326618, XM_009293, gen.XM_009293
Figure 5339: DNA326619, XM_038146, gen.XM_038146
Figure 5340: PRO82975
Figure 5341: DNA326620, XM_092046, gen.XM_092046
Figure 5342: PRO82976
Figure 5343: DNA326621, XM_038098, gen.XM_038098
Figure 5344: PRO82977
Figure 5345: DNA326622, NM_032627, gen.NM_032627
Figure 5346: PRO82978
Figure 5347: DNA326623, XM_165960, gen.XM_165960
Figure 5348: PRO82979
Figure 5349: DNA326624, XM_114004, gen.XM_114004
Figure 5350: DNA326625, NM_012181, gen.NM_012181
Figure 5351: PRO82980
Figure 5352: DNA227249, NM_007263, gen.NM_007263
Figure 5353: PRO37712
Figure 5354: DNA326626, XM_018515, gen.XM_018515
Figure 5355: DNA326627, NM_033415, gen.NM_033415
Figure 5356: PRO82982
Figure 5357: DNA326628, XM_009330, gen.XM_009330
Figure 5358: DNA326629, NM_134440, gen.NM_134440
Figure 5359: PRO82983
Figure 5360: DNA326630, NM_003721, gen.NM_003721
Figure 5361: PRO59220
Figure 5362: DNA326631, NM_015965, gen.NM_015965
Figure 5363: PRO82984
Figure 5364: DNA326632, XM_016378, gen.XM_016378
Figure 5365: PRO82985
Figure 5366: DNA326633, XM_114027, gen.XM_114027
Figure 5367: DNA326634, XM_165963, gen.XM_165963
Figure 5368: PRO82987
Figure 5369: DNA326635, XM_015769, gen.XM_015769
Figure 5370: DNA326636, XM_012812, gen.XM_012812
Figure 5371: DNA326637, XM_085971, gen.XM_085971
Figure 5372: DNA326638, XM_037662, gen.XM_037662
Figure 5373: PRO82991
Figure 5374: DNA326639, NM_001238, gen.NM_001238
Figure 5375: PRO82992
Figure 5376: DNA326640, NM_057182, gen.NM_057182
Figure 5377: PRO4756
Figure 5378: DNA326641, XM_009180, gen.XM_009180
Figure 5379: DNA326642, XM_117118, gen.XM_117118
Figure 5380: DNA326643, XM_092049, gen.XM_092049
Figure 5381: PRO82995
Figure 5382: DNA326644, XM_028672, gen.XM_028672
Figure 5383: DNA326645, XM_028666, gen.XM_028666

Figure 5384: DNA326646, XM_009338, gen.XM_009338
Figure 5385: DNA326647, XM_048258, gen.XM_048258
Figure 5386: PRO82998
Figure 5387: DNA256836, NM_018468, gen.NM_018468
Figure 5388: PRO51767
Figure 5389: DNA326648, NM_024321, gen.NM_024321
Figure 5390: PRO82999
Figure 5391A-B: DNA326649, XM_049237, gen.XM_049237
Figure 5392: PRO83000
Figure 5393: DNA326650, NM_032635, gen.NM_032635
Figure 5394: PRO23845
Figure 5395: DNA326651, XM_115615, gen.XM_115615
Figure 5396A-B: DNA326652, XM_091984, gen.XM_091984
Figure 5397: PRO83002
Figure 5398: DNA326653, XM_085986, gen.XM_085986
Figure 5399: DNA326654, XM_032285, gen.XM_032285
Figure 5400: PRO83004
Figure 5401: DNA326655, NM_002812, gen.NM_002812
Figure 5402: PRO83005
Figure 5403A-E: DNA326656, XM_029455, gen.XM_029455
Figure 5404: DNA326657, XM_029450, gen.XM_029450
Figure 5405: PRO83007
Figure 5406: DNA326658, XM_009149, gen.XM_009149
Figure 5407: PRO62500
Figure 5408: DNA326659, XM_056602, gen.XM_056602
Figure 5409: DNA326660, NM_012237, gen.NM_012237
Figure 5410: PRO83008
Figure 5411: DNA326661, NM_030593, gen.NM_030593
Figure 5412: PRO83009
Figure 5413: DNA326662, NM_017827, gen.NM_017827
Figure 5414: PRO83010
Figure 5415: DNA326663, NM_021107, gen.NM_021107
Figure 5416: PRO83011
Figure 5417: DNA326664, NM_033363, gen.NM_033363
Figure 5418: PRO83012
Figure 5419: DNA326665, XM_059045, gen.XM_059045
Figure 5420: PRO83013
Figure 5421: DNA273474, NM_005884, gen.NM_005884
Figure 5422: PRO61458
Figure 5423: DNA326666, XM_046090, gen.XM_046090
Figure 5424: PRO83014
Figure 5425: DNA326667, XM_086004, gen.XM_086004
Figure 5426: DNA272347, NM_001020, gen.NM_001020
Figure 5427: PRO60603
Figure 5428A-B: DNA326668, NM_003169, gen.NM_003169
Figure 5429: PRO12822
Figure 5430: DNA326669, XM_053074, gen.XM_053074
Figure 5431: PRO83016
Figure 5432: DNA326670, NM_016941, gen.NM_016941
Figure 5433: PRO83017
Figure 5434: DNA256840, NM_004714, gen.NM_004714
Figure 5435: PRO51771
Figure 5436: DNA326671, NM_001436, gen.NM_001436
Figure 5437: PRO83018
Figure 5438: DNA326672, XM_016410, gen.XM_016410
Figure 5439: DNA326673, XM_012860, gen.XM_012860
Figure 5440: DNA326674, XM_097365, gen.XM_097365
Figure 5441: DNA274139, NM_006503, gen.NM_006503
Figure 5442: PRO62075
Figure 5443: DNA326675, XM_009203, gen.XM_009203
Figure 5444: DNA326676, XM_047409, gen.XM_047409
Figure 5445: DNA326677, XM_047376, gen.XM_047376
Figure 5446A-B: DNA326678, XM_047374, gen.XM_047374
Figure 5447: DNA326679, XM_059052, gen.XM_059052
Figure 5448: DNA273600, NM_004596, gen.NM_004596
Figure 5449: PRO61575
Figure 5450: DNA326680, XM_030914, gen.XM_030914
Figure 5451: DNA326681, NM_052848, gen.NM_052848
Figure 5452: PRO83027
Figure 5453: DNA326682, XM_008912,

gen.XM_008912
 Figure 5454: DNA326683, NM_020158,
 gen.NM_020158
 Figure 5455: PRO83029
 Figure 5456: DNA326684, XM_030901,
 gen.XM_030901
 Figure 5457: PRO83030
 Figure 5458: DNA326685, NM_018035,
 gen.NM_018035
 Figure 5459: PRO83031
 Figure 5460: DNA326686, XM_085874,
 gen.XM_085874
 Figure 5461: DNA326687, XM_085875,
 gen.XM_085875
 Figure 5462: DNA326688, XM_085876,
 gen.XM_085876
 Figure 5463: DNA326689, XM_058949,
 gen.XM_058949
 Figure 5464: PRO83035
 Figure 5465: DNA326690, XM_030895,
 gen.XM_030895
 Figure 5466: DNA326691, XM_115603,
 gen.XM_115603
 Figure 5467: PRO83037
 Figure 5468: DNA326692, NM_001022,
 gen.NM_001022
 Figure 5469: PRO83038
 Figure 5470: DNA326693, NM_004706,
 gen.NM_004706
 Figure 5471: PRO83039
 Figure 5472: DNA326694, XM_008878,
 gen.XM_008878
 Figure 5473: PRO83040
 Figure 5474: DNA326695, NM_022752,
 gen.NM_022752
 Figure 5475: PRO83041
 Figure 5476: DNA151808, NM_006494,
 gen.NM_006494
 Figure 5477: PRO12892
 Figure 5478: DNA326696, NM_001816,
 gen.NM_001816
 Figure 5479: PRO34151
 Figure 5480: DNA326697, NM_000554,
 gen.NM_000554
 Figure 5481: PRO83042
 Figure 5482: DNA326698, XM_049920,
 gen.XM_049920
 Figure 5483: DNA326699, XM_055859,
 gen.XM_055859
 Figure 5484A-B: DNA326700, XM_009125,
 gen.XM_009125
 Figure 5485: DNA326701, XM_008860,
 gen.XM_008860
 Figure 5486: DNA326702, XM_009036,
 gen.XM_009036
 Figure 5487: DNA326703, XM_085950,

gen.XM_085950
 Figure 5488: DNA326704, XM_028263,
 gen.XM_028263
 Figure 5489: DNA326705, XM_085928,
 gen.XM_085928
 Figure 5490: PRO36963
 Figure 5491: DNA326706, XM_028267,
 gen.XM_028267
 Figure 5492: DNA326707, NM_013403,
 gen.NM_013403
 Figure 5493: PRO83050
 Figure 5494: DNA103580, NM_001743,
 gen.NM_001743
 Figure 5495: PRO4904
 Figure 5496: DNA326708, XM_009126,
 gen.XM_009126
 Figure 5497: DNA326709, NM_006247,
 gen.NM_006247
 Figure 5498: PRO25881
 Figure 5499: DNA326710, NM_003370,
 gen.NM_003370
 Figure 5500: PRO83052
 Figure 5501: DNA326711, XM_085856,
 gen.XM_085856
 Figure 5502: DNA150784, NM_001983,
 gen.NM_001983
 Figure 5503: PRO12800
 Figure 5504: DNA270931, NM_012099,
 gen.NM_012099
 Figure 5505: PRO59264
 Figure 5506A-B: DNA257531, NM_031417,
 gen.NM_031417
 Figure 5507: PRO52101
 Figure 5508: DNA326712, NM_001294,
 gen.NM_001294
 Figure 5509: PRO83054
 Figure 5510: DNA326713, XM_097274,
 gen.XM_097274
 Figure 5511: DNA88084, NM_000041,
 gen.NM_000041
 Figure 5512: PRO2644
 Figure 5513: DNA256533, NM_006114,
 gen.NM_006114
 Figure 5514: PRO51565
 Figure 5515: DNA251057, NM_002856,
 gen.NM_002856
 Figure 5516: PRO47354
 Figure 5517: DNA226011, NM_005581,
 gen.NM_005581
 Figure 5518: PRO36474
 Figure 5519: DNA326714, NM_012116,
 gen.NM_012116
 Figure 5520: PRO83056
 Figure 5521: DNA326715, XM_097275,
 gen.XM_097275
 Figure 5522: DNA326716, XM_008851,

gen.XM_008851
Figure 5523: DNA274289, NM_016440,
gen.NM_016440
Figure 5524: PRO62212
Figure 5525: DNA326717, NM_012068,
gen.NM_012068
Figure 5526: PRO83059
Figure 5527: DNA326718, XM_085927,
gen.XM_085927
Figure 5528: DNA326719, XM_084023,
gen.XM_084023
Figure 5529: DNA326720, XM_167530,
gen.XM_167530
Figure 5530: DNA326721, XM_114025,
gen.XM_114025
Figure 5531: DNA326722, XM_008985,
gen.XM_008985
Figure 5532: DNA326723, NM_030973,
gen.NM_030973
Figure 5533: PRO83065
Figure 5534: DNA326724, NM_025129,
gen.NM_025129
Figure 5535: PRO83066
Figure 5536: DNA326725, NM_014203,
gen.NM_014203
Figure 5537: DNA326726, XM_085934,
gen.XM_085934
Figure 5538: PRO83068
Figure 5539: DNA326727, NM_001536,
gen.NM_001536
Figure 5540: PRO83069
Figure 5541: DNA326728, XM_165432,
gen.XM_165432
Figure 5542: DNA274823, NM_001571,
gen.NM_001571
Figure 5543: PRO62582
Figure 5544A-B: DNA326729, XM_046313,
gen.XM_046313
Figure 5545: PRO83071
Figure 5546: DNA326730, NM_015953,
gen.NM_015953
Figure 5547: PRO83072
Figure 5548: DNA326731, XM_027904,
gen.XM_027904
Figure 5549: DNA326732, XM_084026,
gen.XM_084026
Figure 5550: DNA290260, NM_012423,
gen.NM_012423
Figure 5551: PRO70385
Figure 5552: DNA326733, XM_058991,
gen.XM_058991
Figure 5553: PRO83073
Figure 5554: DNA326734, NM_017916,
gen.NM_017916
Figure 5555: PRO83074
Figure 5556: DNA326735, NM_003598,

gen.NM_003598
Figure 5557: PRO83075
Figure 5558: DNA326736, NM_006666,
gen.NM_006666
Figure 5559: PRO83076
Figure 5560: DNA326737, XM_114024,
gen.XM_114024
Figure 5561: PRO83077
Figure 5562: DNA304658, NM_000146,
gen.NM_000146
Figure 5563: PRO71085
Figure 5564: DNA326738, NM_004324,
gen.NM_004324
Figure 5565: PRO38101
Figure 5566: DNA326739, NM_006184,
gen.NM_006184
Figure 5567: PRO83078
Figure 5568: DNA273066, NM_001190,
gen.NM_001190
Figure 5569: PRO61129
Figure 5570: DNA326740, XM_058987,
gen.XM_058987
Figure 5571: DNA326741, NM_000979,
gen.NM_000979
Figure 5572: PRO83080
Figure 5573: DNA326742, XM_085935,
gen.XM_085935
Figure 5574: DNA326743, NM_031485,
gen.NM_031485
Figure 5575: PRO61308
Figure 5576: DNA103239, NM_006801,
gen.NM_006801
Figure 5577: PRO4569
Figure 5578: DNA326744, XM_046419,
gen.XM_046419
Figure 5579: PRO83082
Figure 5580: DNA326745, NM_002691,
gen.NM_002691
Figure 5581: PRO83083
Figure 5582: DNA326746, XM_056286,
gen.XM_056286
Figure 5583: PRO83084
Figure 5584: DNA326747, XM_058990,
gen.XM_058990
Figure 5585: PRO83085
Figure 5586: DNA326748, XM_091981,
gen.XM_091981
Figure 5587: PRO83086
Figure 5588: DNA326749, NM_032712,
gen.NM_032712
Figure 5589: PRO23238
Figure 5590: DNA83154, NM_001648,
gen.NM_001648
Figure 5591: PRO2109
Figure 5592: DNA326750, XM_055658,
gen.XM_055658

Figure 5593: DNA269481, NM_001985, gen.NM_001985
Figure 5594: PRO57901
Figure 5595: DNA326751, XM_091886, gen.XM_091886
Figure 5596: PRO83087
Figure 5597: DNA326752, XM_008830, gen.XM_008830
Figure 5598: DNA326753, XM_039908, gen.XM_039908
Figure 5599: PRO83089
Figure 5600: DNA326754, NM_015629, gen.NM_015629
Figure 5601: PRO83090
Figure 5602: DNA326755, XM_050236, gen.XM_050236
Figure 5603: DNA326756, XM_050589, gen.XM_050589
Figure 5604: PRO83092
Figure 5605: DNA326757, XM_117128, gen.XM_117128
Figure 5606: PRO83093
Figure 5607: DNA326758, XM_059321, gen.XM_059321
Figure 5608: DNA326759, NM_003283, gen.NM_003283
Figure 5609: PRO83095
Figure 5610A-B: DNA326760, NM_014931, gen.NM_014931
Figure 5611: PRO83096
Figure 5612: DNA326761, XM_035919, gen.XM_035919
Figure 5613: DNA326762, NM_000991, gen.NM_000991
Figure 5614: PRO83098
Figure 5615: DNA273346, NM_014501, gen.NM_014501
Figure 5616: PRO61349
Figure 5617: DNA326763, NM_013333, gen.NM_013333
Figure 5618: PRO83099
Figure 5619: DNA326764, NM_007279, gen.NM_007279
Figure 5620: PRO83100
Figure 5621: DNA326765, NM_016202, gen.NM_016202
Figure 5622: PRO83101
Figure 5623: DNA326766, XM_034377, gen.XM_034377
Figure 5624: PRO83102
Figure 5625: DNA272062, NM_014453, gen.NM_014453
Figure 5626: PRO60333
Figure 5627: DNA254548, NM_005762, gen.NM_005762
Figure 5628: PRO49653

Figure 5629: DNA326767, XM_085972, gen.XM_085972
Figure 5630: PRO83103
Figure 5631: DNA326768, NM_032792, gen.NM_032792
Figure 5632: PRO83104
Figure 5633: DNA326769, NM_001009, gen.NM_001009
Figure 5634: PRO83105
Figure 5635: DNA326770, XM_058125, gen.XM_058125
Figure 5636: DNA326771, NM_024691, gen.NM_024691
Figure 5637: PRO83107
Figure 5638: DNA297288, NM_021158, gen.NM_021158
Figure 5639: PRO70810
Figure 5640: DNA304662, NM_031229, gen.NM_031229
Figure 5641: PRO71089
Figure 5642: DNA326772, NM_031228, gen.NM_031228
Figure 5643: PRO83108
Figure 5644: DNA326773, XM_097749, gen.XM_097749
Figure 5645: PRO83109
Figure 5646: DNA326774, XM_055993, gen.XM_055993
Figure 5647: DNA326775, XM_009622, gen.XM_009622
Figure 5648: DNA326776, NM_000801, gen.NM_000801
Figure 5649: PRO59142
Figure 5650: DNA326777, NM_054014, gen.NM_054014
Figure 5651: PRO59142
Figure 5652: DNA326778, NM_016143, gen.NM_016143
Figure 5653: PRO83112
Figure 5654: DNA287270, NM_003091, gen.NM_003091
Figure 5655: PRO69541
Figure 5656: DNA326779, NM_052881, gen.NM_052881
Figure 5657: PRO83113
Figure 5658: DNA326780, XM_044914, gen.XM_044914
Figure 5659: PRO83114
Figure 5660: DNA326781, XM_044915, gen.XM_044915
Figure 5661: DNA326782, NM_006899, gen.NM_006899
Figure 5662: PRO83116
Figure 5663: DNA326783, NM_019609, gen.NM_019609
Figure 5664: PRO83117

Figure 5665: DNA326784, NM_021826, gen.NM_021826
 Figure 5666: PRO83118
 Figure 5667: DNA326785, XM_045418, gen.XM_045418
 Figure 5668: DNA287261, NM_017874, gen.NM_017874
 Figure 5669: PRO69533
 Figure 5670: DNA326786, XM_086710, gen.XM_086710
 Figure 5671: DNA326787, XM_045451, gen.XM_045451
 Figure 5672: PRO83121
 Figure 5673: DNA326788, XM_114174, gen.XM_114174
 Figure 5674: DNA326789, XM_045460, gen.XM_045460
 Figure 5675: DNA326790, XM_059268, gen.XM_059268
 Figure 5676A-B: DNA271010, NM_014737, gen.NM_014737
 Figure 5677: PRO59339
 Figure 5678: DNA326791, XM_056035, gen.XM_056035
 Figure 5679: DNA83170, NM_001819, gen.NM_001819
 Figure 5680: PRO2615
 Figure 5681: DNA227348, NM_019095, gen.NM_019095
 Figure 5682: PRO37811
 Figure 5683: DNA326792, NM_003092, gen.NM_003092
 Figure 5684: PRO83125
 Figure 5685: DNA287290, NM_014426, gen.NM_014426
 Figure 5686: PRO69560
 Figure 5687: DNA326793, XM_086701, gen.XM_086701
 Figure 5688: DNA326794, XM_117209, gen.XM_117209
 Figure 5689A-B: DNA326795, XM_046520, gen.XM_046520
 Figure 5690: PRO83128
 Figure 5691: DNA326796, XM_115846, gen.XM_115846
 Figure 5692: PRO83129
 Figure 5693: DNA326797, NM_080820, gen.NM_080820
 Figure 5694: PRO83130
 Figure 5695: DNA326798, XM_086715, gen.XM_086715
 Figure 5696: DNA326799, XM_092760, gen.XM_092760
 Figure 5697: PRO83132
 Figure 5698: DNA326800, NM_012255, gen.NM_012255

Figure 5699: PRO83133
 Figure 5700: DNA326801, XM_012970, gen.XM_012970
 Figure 5701: DNA326802, XM_042765, gen.XM_042765
 Figure 5702: PRO83135
 Figure 5703: DNA150548, NM_001247, gen.NM_001247
 Figure 5704: PRO12324
 Figure 5705A-B: DNA326803, XM_009436, gen.XM_009436
 Figure 5706: DNA326804, XM_114178, gen.XM_114178
 Figure 5707: PRO83137
 Figure 5708: DNA326805, XM_046160, gen.XM_046160
 Figure 5709: PRO83138
 Figure 5710: DNA326806, XM_046179, gen.XM_046179
 Figure 5711: PRO83139
 Figure 5712: DNA326807, XM_086745, gen.XM_086745
 Figure 5713: DNA326808, NM_138578, gen.NM_138578
 Figure 5714: PRO83141
 Figure 5715: DNA326809, NM_012112, gen.NM_012112
 Figure 5716: PRO83142
 Figure 5717: DNA326810, XM_086736, gen.XM_086736
 Figure 5718: PRO83143
 Figure 5719: DNA326811, NM_030815, gen.NM_030815
 Figure 5720: PRO83144
 Figure 5721A-B: DNA150767, NM_014742, gen.NM_014742
 Figure 5722: PRO12460
 Figure 5723A-B: DNA326812, XM_047007, gen.XM_047007
 Figure 5724: PRO83145
 Figure 5725A-B: DNA326813, XM_047011, gen.XM_047011
 Figure 5726: PRO83146
 Figure 5727A-B: DNA326814, XM_047018, gen.XM_047018
 Figure 5728: DNA326815, XM_009450, gen.XM_009450
 Figure 5729: DNA326816, NM_033197, gen.NM_033197
 Figure 5730: PRO83149
 Figure 5731: DNA326817, XM_097772, gen.XM_097772
 Figure 5732: PRO83150
 Figure 5733: DNA326818, NM_016732, gen.NM_016732
 Figure 5734: DNA97298, NM_003908,

gen.NM_003908
 Figure 5735: PRO3645
 Figure 5736: DNA326819, NM_000687, gen.NM_000687
 Figure 5737: PRO83152
 Figure 5738: DNA273517, NM_000178, gen.NM_000178
 Figure 5739: PRO61498
 Figure 5740: DNA326820, NM_018217, gen.NM_018217
 Figure 5741: PRO83153
 Figure 5742: DNA326821, NM_002212, gen.NM_002212
 Figure 5743: PRO60945
 Figure 5744A-C: DNA326822, NM_007186, gen.NM_007186
 Figure 5745: DNA226758, NM_015966, gen.NM_015966
 Figure 5746: PRO37221
 Figure 5747: DNA194701, NM_003915, gen.NM_003915
 Figure 5748: PRO24002
 Figure 5749: DNA326823, XM_113380, gen.XM_113380
 Figure 5750: DNA326824, NM_016558, gen.NM_016558
 Figure 5751: PRO83155
 Figure 5752: DNA326825, NM_015511, gen.NM_015511
 Figure 5753: PRO83156
 Figure 5754: DNA326826, XM_009501, gen.XM_009501
 Figure 5755: PRO83157
 Figure 5756: DNA326827, XM_057236, gen.XM_057236
 Figure 5757: DNA326828, NM_024918, gen.NM_024918
 Figure 5758: PRO83159
 Figure 5759: DNA326829, XM_009642, gen.XM_009642
 Figure 5760: DNA194807, NM_006698, gen.NM_006698
 Figure 5761: PRO24077
 Figure 5762: DNA326830, XM_009686, gen.XM_009686
 Figure 5763: DNA326831, NM_030877, gen.NM_030877
 Figure 5764: PRO83161
 Figure 5765: DNA326832, XM_028806, gen.XM_028806
 Figure 5766A-B: DNA326833, XM_028810, gen.XM_028810
 Figure 5767: PRO83163
 Figure 5768: DNA326834, XM_012931, gen.XM_012931
 Figure 5769: DNA326835, NM_024855, gen.NM_024855
 Figure 5770: PRO83165
 Figure 5771A-B: DNA227472, NM_002660, gen.NM_002660
 Figure 5772: PRO37935
 Figure 5773: DNA326836, XM_097727, gen.XM_097727
 Figure 5774: DNA103525, NM_002466, gen.NM_002466
 Figure 5775: PRO4852
 Figure 5776: DNA326837, XM_029810, gen.XM_029810
 Figure 5777: PRO83167
 Figure 5778: DNA326838, XM_029822, gen.XM_029822
 Figure 5779: DNA326839, NM_002638, gen.NM_002638
 Figure 5780: PRO2065
 Figure 5781: DNA326840, NM_003064, gen.NM_003064
 Figure 5782: PRO1720
 Figure 5783: DNA326841, NM_015937, gen.NM_015937
 Figure 5784: PRO83169
 Figure 5785: DNA273320, NM_007019, gen.NM_007019
 Figure 5786: PRO61327
 Figure 5787: DNA326842, NM_033421, gen.NM_033421
 Figure 5788: PRO83170
 Figure 5789: DNA88569, NM_006227, gen.NM_006227
 Figure 5790: PRO2420
 Figure 5791: DNA88239, NM_004994, gen.NM_004994
 Figure 5792: PRO2711
 Figure 5793: DNA326843, XM_057374, gen.XM_057374
 Figure 5794: DNA326844, XM_114163, gen.XM_114163
 Figure 5795A-B: DNA326845, XM_097731, gen.XM_097731
 Figure 5796A-B: DNA326846, XM_030044, gen.XM_030044
 Figure 5797: PRO83174
 Figure 5798: DNA326847, NM_017895, gen.NM_017895
 Figure 5799: PRO83175
 Figure 5800: DNA326848, XM_097713, gen.XM_097713
 Figure 5801: PRO83176
 Figure 5802: DNA326849, NM_005985, gen.NM_005985
 Figure 5803: PRO83177
 Figure 5804: DNA326850, NM_003349, gen.NM_003349

Figure 5805: PRO83178
Figure 5806: DNA326851, NM_022442, gen.NM_022442
Figure 5807: PRO83179
Figure 5808: DNA326852, NM_005194, gen.NM_005194
Figure 5809: DNA326853, NM_002827, gen.NM_002827
Figure 5810: PRO38066
Figure 5811: DNA326854, NM_003859, gen.NM_003859
Figure 5812: PRO83180
Figure 5813: DNA326855, XM_114165, gen.XM_114165
Figure 5814: DNA269526, NM_001324, gen.NM_001324
Figure 5815: PRO57942
Figure 5816: DNA326856, XM_009549, gen.XM_009549
Figure 5817: PRO83182
Figure 5818: DNA326857, XM_030621, gen.XM_030621
Figure 5819: DNA326858, XM_086648, gen.XM_086648
Figure 5820: PRO83183
Figure 5821: DNA326859, XM_009672, gen.XM_009672
Figure 5822: PRO83184
Figure 5823A-B: DNA326860, XM_009671, gen.XM_009671
Figure 5824: DNA326861, NM_004738, gen.NM_004738
Figure 5825: PRO983
Figure 5826: DNA326862, NM_016592, gen.NM_016592
Figure 5827: PRO83185
Figure 5828: DNA326863, NM_080425, gen.NM_080425
Figure 5829: PRO83186
Figure 5830: DNA304670, NM_000516, gen.NM_000516
Figure 5831: PRO71097
Figure 5832: DNA326864, NM_080426, gen.NM_080426
Figure 5833: PRO83187
Figure 5834: DNA326865, XM_030699, gen.XM_030699
Figure 5835: PRO83188
Figure 5836: DNA188229, NM_000114, gen.NM_000114
Figure 5837: PRO21728
Figure 5838: DNA326866, NM_002792, gen.NM_002792
Figure 5839: PRO83189
Figure 5840A-B: DNA326867, XM_037202, gen.XM_037202
Figure 5841: PRO83190
Figure 5842: DNA326868, XM_037206, gen.XM_037206
Figure 5843: PRO83191
Figure 5844: DNA103486, NM_007002, gen.NM_007002
Figure 5845: PRO4813
Figure 5846A-D: DNA326869, XM_037217, gen.XM_037217
Figure 5847: DNA326870, NM_001024, gen.NM_001024
Figure 5848: PRO83193
Figure 5849: DNA326871, NM_018270, gen.NM_018270
Figure 5850: PRO83194
Figure 5851: DNA326872, XM_028783, gen.XM_028783
Figure 5852: PRO83195
Figure 5853: DNA326873, NM_001853, gen.NM_001853
Figure 5854: PRO83196
Figure 5855: DNA326874, NM_080796, gen.NM_080796
Figure 5856: PRO83197
Figure 5857: DNA326875, NM_022105, gen.NM_022105
Figure 5858: PRO83198
Figure 5859: DNA326876, NM_080797, gen.NM_080797
Figure 5860: PRO83199
Figure 5861: DNA326877, NM_018209, gen.NM_018209
Figure 5862: PRO83200
Figure 5863A-C: DNA326878, XM_028834, gen.XM_028834
Figure 5864: PRO83201
Figure 5865: DNA326879, NM_024299, gen.NM_024299
Figure 5866: PRO83202
Figure 5867A-C: DNA326880, XM_028918, gen.XM_028918
Figure 5868: PRO83203
Figure 5869: DNA326881, NM_032527, gen.NM_032527
Figure 5870: PRO83204
Figure 5871A-B: DNA326882, XM_028966, gen.XM_028966
Figure 5872: PRO83205
Figure 5873: DNA269746, NM_012469, gen.NM_012469
Figure 5874: PRO58155
Figure 5875: DNA326883, XM_114154, gen.XM_114154
Figure 5876: DNA326884, XM_072173, gen.XM_072173
Figure 5877: DNA326885, XM_086759,

gen.XM_086759
Figure 5878: DNA326886, XM_086760, gen.XM_086760
Figure 5879: DNA326887, NM_021219, gen.NM_021219
Figure 5880: PRO28687
Figure 5881: DNA188732, NM_000484, gen.NM_000484
Figure 5882: PRO25302
Figure 5883: DNA326888, NM_016940, gen.NM_016940
Figure 5884: PRO83210
Figure 5885: DNA254572, NM_006585, gen.NM_006585
Figure 5886: PRO49675
Figure 5887: DNA326889, NM_005806, gen.NM_005806
Figure 5888: PRO83211
Figure 5889: DNA326890, XM_114185, gen.XM_114185
Figure 5890: DNA254994, NM_017613, gen.NM_017613
Figure 5891: PRO50083
Figure 5892: DNA274129, NM_001697, gen.NM_001697
Figure 5893: PRO62065
Figure 5894: DNA326891, NM_001757, gen.NM_001757
Figure 5895: PRO83212
Figure 5896A-C: DNA151898, NM_003316, gen.NM_003316
Figure 5897: PRO12135
Figure 5898: DNA326892, NM_003720, gen.NM_003720
Figure 5899: PRO83213
Figure 5900: DNA326893, NM_002606, gen.NM_002606
Figure 5901: PRO83214
Figure 5902: DNA326894, XM_033015, gen.XM_033015
Figure 5903: DNA326895, XM_033016, gen.XM_033016
Figure 5904: PRO59669
Figure 5905: DNA326896, NM_003681, gen.NM_003681
Figure 5906: PRO69486
Figure 5907: DNA326897, XM_035999, gen.XM_035999
Figure 5908: DNA326898, NM_020132, gen.NM_020132
Figure 5909: PRO83217
Figure 5910: DNA326899, XM_036011, gen.XM_036011
Figure 5911: DNA326900, NM_013369, gen.NM_013369
Figure 5912: PRO83219
Figure 5913: DNA326901, XM_036042, gen.XM_036042
Figure 5914: DNA326902, XM_086770, gen.XM_086770
Figure 5915: DNA326903, NM_004928, gen.NM_004928
Figure 5916: PRO83222
Figure 5917: DNA326904, XM_036087, gen.XM_036087
Figure 5918: PRO83223
Figure 5919: DNA326905, XM_009805, gen.XM_009805
Figure 5920: PRO83224
Figure 5921: DNA226409, NM_004339, gen.NM_004339
Figure 5922: PRO36872
Figure 5923: DNA326906, XM_036107, gen.XM_036107
Figure 5924A-B: DNA326907, XM_036175, gen.XM_036175
Figure 5925: DNA326908, XM_097817, gen.XM_097817
Figure 5926A-B: DNA326909, XM_054566, gen.XM_054566
Figure 5927: DNA326910, XM_036755, gen.XM_036755
Figure 5928: DNA326911, XM_086773, gen.XM_086773
Figure 5929: DNA326912, XM_097807, gen.XM_097807
Figure 5930: DNA326913, XM_086777, gen.XM_086777
Figure 5931: DNA326914, NM_002340, gen.NM_002340
Figure 5932: PRO83233
Figure 5933A-B: DNA326915, NM_003906, gen.NM_003906
Figure 5934: PRO83234
Figure 5935: DNA226617, NM_006272, gen.NM_006272
Figure 5936: PRO37080
Figure 5937: DNA326916, NM_033070, gen.NM_033070
Figure 5938: PRO83235
Figure 5939: DNA255046, NM_017829, gen.NM_017829
Figure 5940: PRO50134
Figure 5941: DNA326917, NM_001696, gen.NM_001696
Figure 5942: PRO83236
Figure 5943A-B: DNA326918, XM_032996, gen.XM_032996
Figure 5944: PRO83237
Figure 5945: DNA326919, XM_167538, gen.XM_167538
Figure 5946: DNA326920, XM_033090,

gen.XM_033090
Figure 5947: DNA225954, NM_000407, gen.NM_000407
Figure 5948: PRO36417
Figure 5949: DNA326921, XM_058918, gen.XM_058918
Figure 5950: DNA326922, XM_097833, gen.XM_097833
Figure 5951: DNA326923, NM_024627, gen.NM_024627
Figure 5952: PRO83242
Figure 5953: DNA326924, XM_086809, gen.XM_086809
Figure 5954: DNA326925, NM_006440, gen.NM_006440
Figure 5955: PRO83244
Figure 5956: DNA226561, NM_000754, gen.NM_000754
Figure 5957: PRO37024
Figure 5958: DNA326926, NM_007310, gen.NM_007310
Figure 5959: PRO83245
Figure 5960A-B: DNA326927, XM_033813, gen.XM_033813
Figure 5961: DNA326928, NM_022727, gen.NM_022727
Figure 5962: PRO83247
Figure 5963: DNA326929, XM_086805, gen.XM_086805
Figure 5964: DNA326930, XM_086873, gen.XM_086873
Figure 5965: DNA257549, NM_030573, gen.NM_030573
Figure 5966: PRO52119
Figure 5967: DNA326931, XM_096155, gen.XM_096155
Figure 5968: DNA326932, XM_096156, gen.XM_096156
Figure 5969A-B: DNA326933, XM_036937, gen.XM_036937
Figure 5970: PRO83252
Figure 5971: DNA326934, XM_097886, gen.XM_097886
Figure 5972: PRO83253
Figure 5973: DNA304835, NM_022044, gen.NM_022044
Figure 5974: PRO71242
Figure 5975: DNA326935, NM_006115, gen.NM_006115
Figure 5976: PRO37012
Figure 5977: DNA326936, XM_037682, gen.XM_037682
Figure 5978: PRO83254
Figure 5979: DNA326937, NM_002415, gen.NM_002415
Figure 5980: PRO83255

Figure 5981A-B: DNA326938, XM_037797, gen.XM_037797
Figure 5982: PRO83256
Figure 5983: DNA326939, NM_004175, gen.NM_004175
Figure 5984: PRO83257
Figure 5985: DNA326940, XM_086821, gen.XM_086821
Figure 5986: DNA326941, XM_092888, gen.XM_092888
Figure 5987: DNA326942, NM_005080, gen.NM_005080
Figure 5988: PRO83260
Figure 5989: DNA269830, NM_005243, gen.NM_005243
Figure 5990: PRO58232
Figure 5991: DNA326943, NM_006478, gen.NM_006478
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DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTSI. Definitions

The terms "TAT polypeptide" and "TAT" as used herein and when immediately followed by a numerical designation, refer to various polypeptides, wherein the complete designation (i.e., TAT/number) refers to specific polypeptide sequences as described herein. The terms "TAT/number polypeptide" and "TAT/number" wherein the term "number" is provided as an actual numerical designation as used herein encompass native sequence polypeptides, polypeptide variants and fragments of native sequence polypeptides and polypeptide variants (which are further defined herein). The TAT polypeptides described herein may be isolated from a variety of sources, such as from human tissue types or from another source, or prepared by recombinant or synthetic methods. The term "TAT polypeptide" refers to each individual TAT/number polypeptide disclosed herein. All disclosures in this specification which refer to the "TAT polypeptide" refer to each of the polypeptides individually as well as jointly. For example, descriptions of the preparation of, purification of, derivation of, formation of antibodies to or against, formation of TAT binding oligopeptides to or against, formation of TAT binding organic molecules to or against, administration of, compositions containing, treatment of a disease with, etc., pertain to each polypeptide of the invention individually. The term "TAT polypeptide" also includes variants of the TAT/number polypeptides disclosed herein.

A "native sequence TAT polypeptide" comprises a polypeptide having the same amino acid sequence as the corresponding TAT polypeptide derived from nature. Such native sequence TAT polypeptides can be isolated from nature or can be produced by recombinant or synthetic means. The term "native sequence TAT polypeptide" specifically encompasses naturally-occurring truncated or secreted forms of the specific TAT polypeptide (e.g., an extracellular domain sequence), naturally-occurring variant forms (e.g., alternatively spliced forms) and naturally-occurring allelic variants of the polypeptide. In certain embodiments of the invention, the native sequence TAT polypeptides disclosed herein are mature or full-length native sequence polypeptides comprising the full-length amino acids sequences shown in the accompanying figures. Start and stop codons (if indicated) are shown in bold font and underlined in the figures. Nucleic acid residues indicated as "N" in the accompanying figures are any nucleic acid residue. However, while the TAT polypeptides disclosed in the accompanying figures are shown to begin with methionine residues designated herein as amino acid position 1 in the figures, it is conceivable and possible that other methionine residues located either upstream or downstream from the amino acid position 1 in the figures may be employed as the starting amino acid residue for the TAT polypeptides.

The TAT polypeptide "extracellular domain" or "ECD" refers to a form of the TAT polypeptide which is essentially free of the transmembrane and cytoplasmic domains. Ordinarily, a TAT polypeptide ECD will have less than 1% of such transmembrane and/or cytoplasmic domains and preferably, will have less than 0.5% of such domains. It will be understood that any transmembrane domains identified for the TAT polypeptides of the present invention are identified pursuant to criteria routinely employed in the art for identifying that type of hydrophobic domain. The exact boundaries of a transmembrane domain may vary but most likely by no more than about 5 amino acids at either end of the domain as initially identified herein. Optionally, therefore, an

extracellular domain of a TAT polypeptide may contain from about 5 or fewer amino acids on either side of the transmembrane domain/extracellular domain boundary as identified in the Examples or specification and such polypeptides, with or without the associated signal peptide, and nucleic acid encoding them, are contemplated by the present invention.

The approximate location of the "signal peptides" of the various TAT polypeptides disclosed herein may be shown in the present specification and/or the accompanying figures. It is noted, however, that the C-terminal boundary of a signal peptide may vary, but most likely by no more than about 5 amino acids on either side of the signal peptide C-terminal boundary as initially identified herein, wherein the C-terminal boundary of the signal peptide may be identified pursuant to criteria routinely employed in the art for identifying that type of amino acid sequence element (e.g., Nielsen et al., Prot. Eng. 10:1-6 (1997) and von Heinje et al., Nucl. Acids. Res. 14:4683-4690 (1986)). Moreover, it is also recognized that, in some cases, cleavage of a signal sequence from a secreted polypeptide is not entirely uniform, resulting in more than one secreted species. These mature polypeptides, where the signal peptide is cleaved within no more than about 5 amino acids on either side of the C-terminal boundary of the signal peptide as identified herein, and the polynucleotides encoding them, are contemplated by the present invention.

"TAT polypeptide variant" means a TAT polypeptide, preferably an active TAT polypeptide, as defined herein having at least about 80% amino acid sequence identity with a full-length native sequence TAT polypeptide sequence as disclosed herein, a TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length TAT polypeptide sequence as disclosed herein (such as those encoded by a nucleic acid that represents only a portion of the complete coding sequence for a full-length TAT polypeptide). Such TAT polypeptide variants include, for instance, TAT polypeptides wherein one or more amino acid residues are added, or deleted, at the N- or C-terminus of the full-length native amino acid sequence. Ordinarily, a TAT polypeptide variant will have at least about 80% amino acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% amino acid sequence identity, to a full-length native sequence TAT polypeptide sequence as disclosed herein, a TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal peptide, as disclosed herein or any other specifically defined fragment of a full-length TAT polypeptide sequence as disclosed herein. Ordinarily, TAT variant polypeptides are at least about 10 amino acids in length, alternatively at least about 20, 30, 40, 50, 60, 70, 80, 90, 100, 110, 120, 130, 140, 150, 160, 170, 180, 190, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600 amino acids in length, or more. Optionally, TAT variant polypeptides will have no more than one conservative amino acid substitution as compared to the native TAT polypeptide sequence, alternatively no more than 2, 3, 4, 5, 6, 7, 8, 9, or 10 conservative amino acid substitution as compared to the native TAT polypeptide sequence.

"Percent (%) amino acid sequence identity" with respect to the TAT polypeptide sequences identified

herein is defined as the percentage of amino acid residues in a candidate sequence that are identical with the amino acid residues in the specific TAT polypeptide sequence, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity, and not considering any conservative substitutions as part of the sequence identity. Alignment for purposes of determining percent amino acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly 5 available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. Those skilled in the art can determine appropriate parameters for measuring alignment, including any algorithms needed to achieve maximal alignment over the full length of the sequences being compared. For purposes herein, however, % amino acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below.

10 The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating 15 system, preferably digital UNIX V4.0D. All sequence comparison parameters are set by the ALIGN-2 program and do not vary.

20 In situations where ALIGN-2 is employed for amino acid sequence comparisons, the % amino acid sequence identity of a given amino acid sequence A to, with, or against a given amino acid sequence B (which can alternatively be phrased as a given amino acid sequence A that has or comprises a certain % amino acid sequence identity to, with, or against a given amino acid sequence B) is calculated as follows:

$$100 \text{ times the fraction } X/Y$$

25 where X is the number of amino acid residues scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of A and B, and where Y is the total number of amino acid residues in B. It will be appreciated that where the length of amino acid sequence A is not equal to the length of amino acid sequence B, the % amino acid sequence identity of A to B will not equal the % amino acid sequence identity of B to A. As examples of % amino acid sequence identity calculations using this method, Tables 2 and 3 demonstrate how to calculate the % amino acid sequence identity of the amino acid sequence designated 30 "Comparison Protein" to the amino acid sequence designated "TAT", wherein "TAT" represents the amino acid sequence of a hypothetical TAT polypeptide of interest, "Comparison Protein" represents the amino acid sequence of a polypeptide against which the "TAT" polypeptide of interest is being compared, and "X", "Y" and "Z" each represent different hypothetical amino acid residues. Unless specifically stated otherwise, all % amino acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using 35 the ALIGN-2 computer program.

"TAT variant polynucleotide" or "TAT variant nucleic acid sequence" means a nucleic acid molecule

which encodes a TAT polypeptide, preferably an active TAT polypeptide, as defined herein and which has at least about 80% nucleic acid sequence identity with a nucleotide acid sequence encoding a full-length native sequence TAT polypeptide sequence as disclosed herein, a full-length native sequence TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal peptide, as disclosed herein or any other fragment of a full-length TAT polypeptide sequence as disclosed herein (such as those encoded by a nucleic acid that represents only a portion of the complete coding sequence for a full-length TAT polypeptide). Ordinarily, a TAT variant polynucleotide will have at least about 80% nucleic acid sequence identity, alternatively at least about 81%, 82%, 83%, 84%, 85%, 86%, 87%, 88%, 89%, 90%, 91%, 92%, 93%, 94%, 95%, 96%, 97%, 98%, or 99% nucleic acid sequence identity with a nucleic acid sequence encoding a full-length native sequence TAT polypeptide sequence as disclosed herein, a full-length native sequence TAT polypeptide sequence lacking the signal peptide as disclosed herein, an extracellular domain of a TAT polypeptide, with or without the signal sequence, as disclosed herein or any other fragment of a full-length TAT polypeptide sequence as disclosed herein. Variants do not encompass the native nucleotide sequence.

Ordinarily, TAT variant polynucleotides are at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710, 720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length.

"Percent (%) nucleic acid sequence identity" with respect to TAT-encoding nucleic acid sequences identified herein is defined as the percentage of nucleotides in a candidate sequence that are identical with the nucleotides in the TAT nucleic acid sequence of interest, after aligning the sequences and introducing gaps, if necessary, to achieve the maximum percent sequence identity. Alignment for purposes of determining percent nucleic acid sequence identity can be achieved in various ways that are within the skill in the art, for instance, using publicly available computer software such as BLAST, BLAST-2, ALIGN or Megalign (DNASTAR) software. For purposes herein, however, % nucleic acid sequence identity values are generated using the sequence comparison computer program ALIGN-2, wherein the complete source code for the ALIGN-2 program is provided in Table 1 below. The ALIGN-2 sequence comparison computer program was authored by Genentech, Inc. and the source code shown in Table 1 below has been filed with user documentation in the U.S. Copyright Office, Washington D.C., 20559, where it is registered under U.S. Copyright Registration No. TXU510087. The ALIGN-2 program is publicly available through Genentech, Inc., South San Francisco, California or may be compiled from the source code provided in Table 1 below. The ALIGN-2 program should be compiled for use on a UNIX operating system, preferably digital UNIX V4.0D. All sequence comparison

parameters are set by the ALIGN-2 program and do not vary.

In situations where ALIGN-2 is employed for nucleic acid sequence comparisons, the % nucleic acid sequence identity of a given nucleic acid sequence C to, with, or against a given nucleic acid sequence D (which can alternatively be phrased as a given nucleic acid sequence C that has or comprises a certain % nucleic acid sequence identity to, with, or against a given nucleic acid sequence D) is calculated as follows:

5

$$100 \text{ times the fraction } W/Z$$

where W is the number of nucleotides scored as identical matches by the sequence alignment program ALIGN-2 in that program's alignment of C and D, and where Z is the total number of nucleotides in D. It will be appreciated that where the length of nucleic acid sequence C is not equal to the length of nucleic acid sequence D, the % nucleic acid sequence identity of C to D will not equal the % nucleic acid sequence identity of D to C. As examples of % nucleic acid sequence identity calculations, Tables 4 and 5, demonstrate how to calculate the % nucleic acid sequence identity of the nucleic acid sequence designated "Comparison DNA" to the nucleic acid sequence designated "TAT-DNA", wherein "TAT-DNA" represents a hypothetical TAT-encoding nucleic acid sequence of interest, "Comparison DNA" represents the nucleotide sequence of a nucleic acid molecule against which the "TAT-DNA" nucleic acid molecule of interest is being compared, and "N", "L" and "V" each represent different hypothetical nucleotides. Unless specifically stated otherwise, all % nucleic acid sequence identity values used herein are obtained as described in the immediately preceding paragraph using the ALIGN-2 computer program.

20 In other embodiments, TAT variant polynucleotides are nucleic acid molecules that encode a TAT polypeptide and which are capable of hybridizing, preferably under stringent hybridization and wash conditions, to nucleotide sequences encoding a full-length TAT polypeptide as disclosed herein. TAT variant polypeptides may be those that are encoded by a TAT variant polynucleotide.

25 The term "full-length coding region" when used in reference to a nucleic acid encoding a TAT polypeptide refers to the sequence of nucleotides which encode the full-length TAT polypeptide of the invention (which is often shown between start and stop codons, inclusive thereof, in the accompanying figures). The term "full-length coding region" when used in reference to an ATCC deposited nucleic acid refers to the TAT polypeptide-encoding portion of the cDNA that is inserted into the vector deposited with the ATCC (which is often shown between start and stop codons, inclusive thereof, in the accompanying figures).

30 "Isolated," when used to describe the various TAT polypeptides disclosed herein, means polypeptide that has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials that would typically interfere with diagnostic or therapeutic uses for the polypeptide, and may include enzymes, hormones, and other proteinaceous or non-proteinaceous solutes. In preferred embodiments, the polypeptide will be purified (1) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (2) to homogeneity by SDS-PAGE under non-reducing or reducing conditions using Coomassie blue or,

preferably, silver stain. Isolated polypeptide includes polypeptide *in situ* within recombinant cells, since at least one component of the TAT polypeptide natural environment will not be present. Ordinarily, however, isolated polypeptide will be prepared by at least one purification step.

An "isolated" TAT polypeptide-encoding nucleic acid or other polypeptide-encoding nucleic acid is a nucleic acid molecule that is identified and separated from at least one contaminant nucleic acid molecule with which it is ordinarily associated in the natural source of the polypeptide-encoding nucleic acid. An isolated polypeptide-encoding nucleic acid molecule is other than in the form or setting in which it is found in nature. Isolated polypeptide-encoding nucleic acid molecules therefore are distinguished from the specific polypeptide-encoding nucleic acid molecule as it exists in natural cells. However, an isolated polypeptide-encoding nucleic acid molecule includes polypeptide-encoding nucleic acid molecules contained in cells that ordinarily express the polypeptide where, for example, the nucleic acid molecule is in a chromosomal location different from that of natural cells.

The term "control sequences" refers to DNA sequences necessary for the expression of an operably linked coding sequence in a particular host organism. The control sequences that are suitable for prokaryotes, for example, include a promoter, optionally an operator sequence, and a ribosome binding site. Eukaryotic cells are known to utilize promoters, polyadenylation signals, and enhancers.

Nucleic acid is "operably linked" when it is placed into a functional relationship with another nucleic acid sequence. For example, DNA for a presequence or secretory leader is operably linked to DNA for a polypeptide if it is expressed as a preprotein that participates in the secretion of the polypeptide; a promoter or enhancer is operably linked to a coding sequence if it affects the transcription of the sequence; or a ribosome binding site is operably linked to a coding sequence if it is positioned so as to facilitate translation. Generally, "operably linked" means that the DNA sequences being linked are contiguous, and, in the case of a secretory leader, contiguous and in reading phase. However, enhancers do not have to be contiguous. Linking is accomplished by ligation at convenient restriction sites. If such sites do not exist, the synthetic oligonucleotide adaptors or linkers are used in accordance with conventional practice.

"Stringency" of hybridization reactions is readily determinable by one of ordinary skill in the art, and generally is an empirical calculation dependent upon probe length, washing temperature, and salt concentration. In general, longer probes require higher temperatures for proper annealing, while shorter probes need lower temperatures. Hybridization generally depends on the ability of denatured DNA to reanneal when complementary strands are present in an environment below their melting temperature. The higher the degree of desired homology between the probe and hybridizable sequence, the higher the relative temperature which can be used. As a result, it follows that higher relative temperatures would tend to make the reaction conditions more stringent, while lower temperatures less so. For additional details and explanation of stringency of hybridization reactions, see Ausubel et al., Current Protocols in Molecular Biology, Wiley Interscience Publishers, (1995).

"Stringent conditions" or "high stringency conditions", as defined herein, may be identified by those that: (1) employ low ionic strength and high temperature for washing, for example 0.015 M sodium

chloride/0.0015 M sodium citrate/0.1% sodium dodecyl sulfate at 50°C; (2) employ during hybridization a denaturing agent, such as formamide, for example, 50% (v/v) formamide with 0.1% bovine serum albumin/0.1% Ficoll/0.1% polyvinylpyrrolidone/50mM sodium phosphate buffer at pH 6.5 with 750 mM sodium chloride, 75 mM sodium citrate at 42°C; or (3) overnight hybridization in a solution that employs 50% formamide, 5 x SSC (0.75 M NaCl, 0.075 M sodium citrate), 50 mM sodium phosphate (pH 6.8), 0.1% sodium pyrophosphate, 5 x Denhardt's solution, sonicated salmon sperm DNA (50 µg/ml), 0.1% SDS, and 10% dextran sulfate at 42°C, with a 10 minute wash at 42°C in 0.2 x SSC (sodium chloride/sodium citrate) followed by a 10 minute high-stringency wash consisting of 0.1 x SSC containing EDTA at 55°C.

"Moderately stringent conditions" may be identified as described by Sambrook et al., Molecular Cloning: A Laboratory Manual, New York: Cold Spring Harbor Press, 1989, and include the use of washing 10 solution and hybridization conditions (e.g., temperature, ionic strength and %SDS) less stringent than those described above. An example of moderately stringent conditions is overnight incubation at 37°C in a solution comprising: 20% formamide, 5 x SSC (150 mM NaCl, 15 mM trisodium citrate), 50 mM sodium phosphate (pH 7.6), 5 x Denhardt's solution, 10% dextran sulfate, and 20 mg/ml denatured sheared salmon sperm DNA, followed by washing the filters in 1 x SSC at about 37-50°C. The skilled artisan will recognize how to adjust 15 the temperature, ionic strength, etc. as necessary to accommodate factors such as probe length and the like.

The term "epitope tagged" when used herein refers to a chimeric polypeptide comprising a TAT polypeptide or anti-TAT antibody fused to a "tag polypeptide". The tag polypeptide has enough residues to provide an epitope against which an antibody can be made, yet is short enough such that it does not interfere with activity of the polypeptide to which it is fused. The tag polypeptide preferably also is fairly unique so that the antibody does not substantially cross-react with other epitopes. Suitable tag polypeptides generally have at 20 least six amino acid residues and usually between about 8 and 50 amino acid residues (preferably, between about 10 and 20 amino acid residues).

"Active" or "activity" for the purposes herein refers to form(s) of a TAT polypeptide which retain a 25 biological and/or an immunological activity of native or naturally-occurring TAT, wherein "biological" activity refers to a biological function (either inhibitory or stimulatory) caused by a native or naturally-occurring TAT other than the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring TAT and an "immunological" activity refers to the ability to induce the production of an antibody against an antigenic epitope possessed by a native or naturally-occurring TAT.

The term "antagonist" is used in the broadest sense, and includes any molecule that partially or fully 30 blocks, inhibits, or neutralizes a biological activity of a native TAT polypeptide disclosed herein. In a similar manner, the term "agonist" is used in the broadest sense and includes any molecule that mimics a biological activity of a native TAT polypeptide disclosed herein. Suitable agonist or antagonist molecules specifically include agonist or antagonist antibodies or antibody fragments, fragments or amino acid sequence variants of native TAT polypeptides, peptides, antisense oligonucleotides, small organic molecules, etc. Methods for 35 identifying agonists or antagonists of a TAT polypeptide may comprise contacting a TAT polypeptide with a candidate agonist or antagonist molecule and measuring a detectable change in one or more biological activities

normally associated with the TAT polypeptide.

"Treating" or "treatment" or "alleviation" refers to both therapeutic treatment and prophylactic or preventative measures, wherein the object is to prevent or slow down (lessen) the targeted pathologic condition or disorder. Those in need of treatment include those already with the disorder as well as those prone to have the disorder or those in whom the disorder is to be prevented. A subject or mammal is successfully "treated" 5 for a TAT polypeptide-expressing cancer if, after receiving a therapeutic amount of an anti-TAT antibody, TAT binding oligopeptide or TAT binding organic molecule according to the methods of the present invention, the patient shows observable and/or measurable reduction in or absence of one or more of the following: reduction in the number of cancer cells or absence of the cancer cells; reduction in the tumor size; inhibition (i.e., slow to some extent and preferably stop) of cancer cell infiltration into peripheral organs including the spread of 10 cancer into soft tissue and bone; inhibition (i.e., slow to some extent and preferably stop) of tumor metastasis; inhibition, to some extent, of tumor growth; and/or relief to some extent, one or more of the symptoms associated with the specific cancer; reduced morbidity and mortality, and improvement in quality of life issues. To the extent the anti-TAT antibody or TAT binding oligopeptide may prevent growth and/or kill existing cancer 15 cells, it may be cytostatic and/or cytotoxic. Reduction of these signs or symptoms may also be felt by the patient.

The above parameters for assessing successful treatment and improvement in the disease are readily measurable by routine procedures familiar to a physician. For cancer therapy, efficacy can be measured, for example, by assessing the time to disease progression (TTP) and/or determining the response rate (RR). Metastasis can be determined by staging tests and by bone scan and tests for calcium level and other enzymes 20 to determine spread to the bone. CT scans can also be done to look for spread to the pelvis and lymph nodes in the area. Chest X-rays and measurement of liver enzyme levels by known methods are used to look for metastasis to the lungs and liver, respectively. Other routine methods for monitoring the disease include transrectal ultrasonography (TRUS) and transrectal needle biopsy (TRNB).

For bladder cancer, which is a more localized cancer, methods to determine progress of disease include 25 urinary cytologic evaluation by cystoscopy, monitoring for presence of blood in the urine, visualization of the urothelial tract by sonography or an intravenous pyelogram, computed tomography (CT) and magnetic resonance imaging (MRI). The presence of distant metastases can be assessed by CT of the abdomen, chest x-rays, or radionuclide imaging of the skeleton.

"Chronic" administration refers to administration of the agent(s) in a continuous mode as opposed to 30 an acute mode, so as to maintain the initial therapeutic effect (activity) for an extended period of time. "Intermittent" administration is treatment that is not consecutively done without interruption, but rather is cyclic in nature.

"Mammal" for purposes of the treatment of, alleviating the symptoms of or diagnosis of a cancer refers 35 to any animal classified as a mammal, including humans, domestic and farm animals, and zoo, sports, or pet animals, such as dogs, cats, cattle, horses, sheep, pigs, goats, rabbits, etc. Preferably, the mammal is human.

Administration "in combination with" one or more further therapeutic agents includes simultaneous

(concurrent) and consecutive administration in any order.

"Carriers" as used herein include pharmaceutically acceptable carriers, excipients, or stabilizers which are nontoxic to the cell or mammal being exposed thereto at the dosages and concentrations employed. Often the physiologically acceptable carrier is an aqueous pH buffered solution. Examples of physiologically acceptable carriers include buffers such as phosphate, citrate, and other organic acids; antioxidants including ascorbic acid; low molecular weight (less than about 10 residues) polypeptide; proteins, such as serum albumin, gelatin, or immunoglobulins; hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, arginine or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrins; chelating agents such as EDTA; sugar alcohols such as mannitol or sorbitol; salt-forming counterions such as sodium; and/or nonionic surfactants such as TWEEN®, polyethylene glycol (PEG), and PLURONICS®.

By "solid phase" or "solid support" is meant a non-aqueous matrix to which an antibody, TAT binding oligopeptide or TAT binding organic molecule of the present invention can adhere or attach. Examples of solid phases encompassed herein include those formed partially or entirely of glass (e.g., controlled pore glass), polysaccharides (e.g., agarose), polyacrylamides, polystyrene, polyvinyl alcohol and silicones. In certain embodiments, depending on the context, the solid phase can comprise the well of an assay plate; in others it is a purification column (e.g., an affinity chromatography column). This term also includes a discontinuous solid phase of discrete particles, such as those described in U.S. Patent No. 4,275,149.

A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug (such as a TAT polypeptide, an antibody thereto or a TAT binding oligopeptide) to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes.

A "small" molecule or "small" organic molecule is defined herein to have a molecular weight below about 500 Daltons.

An "effective amount" of a polypeptide, antibody, TAT binding oligopeptide, TAT binding organic molecule or an agonist or antagonist thereof as disclosed herein is an amount sufficient to carry out a specifically stated purpose. An "effective amount" may be determined empirically and in a routine manner, in relation to the stated purpose.

The term "therapeutically effective amount" refers to an amount of an antibody, polypeptide, TAT binding oligopeptide, TAT binding organic molecule or other drug effective to "treat" a disease or disorder in a subject or mammal. In the case of cancer, the therapeutically effective amount of the drug may reduce the number of cancer cells; reduce the tumor size; inhibit (i.e., slow to some extent and preferably stop) cancer cell infiltration into peripheral organs; inhibit (i.e., slow to some extent and preferably stop) tumor metastasis; inhibit, to some extent, tumor growth; and/or relieve to some extent one or more of the symptoms associated with the cancer. See the definition herein of "treating". To the extent the drug may prevent growth and/or kill existing cancer cells, it may be cytostatic and/or cytotoxic.

A "growth inhibitory amount" of an anti-TAT antibody, TAT polypeptide, TAT binding oligopeptide

or TAT binding organic molecule is an amount capable of inhibiting the growth of a cell, especially tumor, e.g., cancer cell, either *in vitro* or *in vivo*. A "growth inhibitory amount" of an anti-TAT antibody, TAT polypeptide, TAT binding oligopeptide or TAT binding organic molecule for purposes of inhibiting neoplastic cell growth may be determined empirically and in a routine manner.

5 A "cytotoxic amount" of an anti-TAT antibody, TAT polypeptide, TAT binding oligopeptide or TAT binding organic molecule is an amount capable of causing the destruction of a cell, especially tumor, e.g., cancer cell, either *in vitro* or *in vivo*. A "cytotoxic amount" of an anti-TAT antibody, TAT polypeptide, TAT binding oligopeptide or TAT binding organic molecule for purposes of inhibiting neoplastic cell growth may be determined empirically and in a routine manner.

10 The term "antibody" is used in the broadest sense and specifically covers, for example, single anti-TAT monoclonal antibodies (including agonist, antagonist, and neutralizing antibodies), anti-TAT antibody compositions with polyepitopic specificity, polyclonal antibodies, single chain anti-TAT antibodies, and fragments of anti-TAT antibodies (see below) as long as they exhibit the desired biological or immunological activity. The term "immunoglobulin" (Ig) is used interchangeable with antibody herein.

15 An "isolated antibody" is one which has been identified and separated and/or recovered from a component of its natural environment. Contaminant components of its natural environment are materials which would interfere with diagnostic or therapeutic uses for the antibody, and may include enzymes, hormones, and other proteinaceous or nonproteinaceous solutes. In preferred embodiments, the antibody will be purified (1) to greater than 95% by weight of antibody as determined by the Lowry method, and most preferably more than 99% by weight, (2) to a degree sufficient to obtain at least 15 residues of N-terminal or internal amino acid sequence by use of a spinning cup sequenator, or (3) to homogeneity by SDS-PAGE under reducing or nonreducing conditions using Coomassie blue or, preferably, silver stain. Isolated antibody includes the antibody *in situ* within recombinant cells since at least one component of the antibody's natural environment will not be present. Ordinarily, however, isolated antibody will be prepared by at least one purification step.

20 The basic 4-chain antibody unit is a heterotetrameric glycoprotein composed of two identical light (L) chains and two identical heavy (H) chains (an IgM antibody consists of 5 of the basic heterotetramer unit along with an additional polypeptide called J chain, and therefore contain 10 antigen binding sites, while secreted IgA antibodies can polymerize to form polyvalent assemblages comprising 2-5 of the basic 4-chain units along with J chain). In the case of IgGs, the 4-chain unit is generally about 150,000 daltons. Each L chain is linked to a H chain by one covalent disulfide bond, while the two H chains are linked to each other by one or more disulfide bonds depending on the H chain isotype. Each H and L chain also has regularly spaced intrachain disulfide bridges. Each H chain has at the N-terminus, a variable domain (V_H) followed by three constant domains (C_H) for each of the α and γ chains and four C_H domains for μ and ϵ isotypes. Each L chain has at the N-terminus, a variable domain (V_L) followed by a constant domain (C_L) at its other end. The V_L is aligned with the V_H and the C_L is aligned with the first constant domain of the heavy chain (C_H1). Particular amino acid residues are believed to form an interface between the light chain and heavy chain variable domains. The pairing of a V_H and V_L together forms a single antigen-binding site. For the structure and properties of the

different classes of antibodies, see, e.g., Basic and Clinical Immunology, 8th edition, Daniel P. Stites, Abba I. Terr and Tristram G. Parslow (eds.), Appleton & Lange, Norwalk, CT, 1994, page 71 and Chapter 6.

The L chain from any vertebrate species can be assigned to one of two clearly distinct types, called kappa and lambda, based on the amino acid sequences of their constant domains. Depending on the amino acid sequence of the constant domain of their heavy chains (C_H), immunoglobulins can be assigned to different classes or isotypes. There are five classes of immunoglobulins: IgA, IgD, IgE, IgG, and IgM, having heavy chains designated α , δ , ϵ , γ , and μ , respectively. The γ and α classes are further divided into subclasses on the basis of relatively minor differences in C_H sequence and function, e.g., humans express the following subclasses: IgG1, IgG2, IgG3, IgG4, IgA1, and IgA2.

The term "variable" refers to the fact that certain segments of the variable domains differ extensively in sequence among antibodies. The V domain mediates antigen binding and define specificity of a particular antibody for its particular antigen. However, the variability is not evenly distributed across the 110-amino acid span of the variable domains. Instead, the V regions consist of relatively invariant stretches called framework regions (FRs) of 15-30 amino acids separated by shorter regions of extreme variability called "hypervariable regions" that are each 9-12 amino acids long. The variable domains of native heavy and light chains each comprise four FRs, largely adopting a β -sheet configuration, connected by three hypervariable regions, which form loops connecting, and in some cases forming part of, the β -sheet structure. The hypervariable regions in each chain are held together in close proximity by the FRs and, with the hypervariable regions from the other chain, contribute to the formation of the antigen-binding site of antibodies (see Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)). The constant domains are not involved directly in binding an antibody to an antigen, but exhibit various effector functions, such as participation of the antibody in antibody dependent cellular cytotoxicity (ADCC).

The term "hypervariable region" when used herein refers to the amino acid residues of an antibody which are responsible for antigen-binding. The hypervariable region generally comprises amino acid residues from a "complementarity determining region" or "CDR" (e.g. around about residues 24-34 (L1), 50-56 (L2) and 89-97 (L3) in the V_L , and around about 1-35 (H1), 50-65 (H2) and 95-102 (H3) in the V_H ; Kabat et al., Sequences of Proteins of Immunological Interest, 5th Ed. Public Health Service, National Institutes of Health, Bethesda, MD. (1991)) and/or those residues from a "hypervariable loop" (e.g. residues 26-32 (L1), 50-52 (L2) and 91-96 (L3) in the V_L , and 26-32 (H1), 53-55 (H2) and 96-101 (H3) in the V_H ; Chothia and Lesk J. Mol. Biol. 196:901-917 (1987)).

The term "monoclonal antibody" as used herein refers to an antibody obtained from a population of substantially homogeneous antibodies, i.e., the individual antibodies comprising the population are identical except for possible naturally occurring mutations that may be present in minor amounts. Monoclonal antibodies are highly specific, being directed against a single antigenic site. Furthermore, in contrast to polyclonal antibody preparations which include different antibodies directed against different determinants (epitopes), each monoclonal antibody is directed against a single determinant on the antigen. In addition to their specificity, the monoclonal antibodies are advantageous in that they may be synthesized uncontaminated by other antibodies.

The modifier "monoclonal" is not to be construed as requiring production of the antibody by any particular method. For example, the monoclonal antibodies useful in the present invention may be prepared by the hybridoma methodology first described by Kohler et al., Nature, 256:495 (1975), or may be made using recombinant DNA methods in bacterial, eukaryotic animal or plant cells (see, e.g., U.S. Patent No. 4,816,567). The "monoclonal antibodies" may also be isolated from phage antibody libraries using the techniques described in Clackson et al., Nature, 352:624-628 (1991) and Marks et al., J. Mol. Biol., 222:581-597 (1991), for example.

5 The monoclonal antibodies herein include "chimeric" antibodies in which a portion of the heavy and/or light chain is identical with or homologous to corresponding sequences in antibodies derived from a particular species or belonging to a particular antibody class or subclass, while the remainder of the chain(s) is identical with or homologous to corresponding sequences in antibodies derived from another species or belonging to another antibody class or subclass, as well as fragments of such antibodies, so long as they exhibit the desired 10 biological activity (see U.S. Patent No. 4,816,567; and Morrison et al., Proc. Natl. Acad. Sci. USA, 81:6851-6855 (1984)). Chimeric antibodies of interest herein include "primatized" antibodies comprising variable domain antigen-binding sequences derived from a non-human primate (e.g. Old World Monkey, Ape etc), and human 15 constant region sequences.

An "intact" antibody is one which comprises an antigen-binding site as well as a C_L and at least heavy chain constant domains, C_H1 , C_H2 and C_H3 . The constant domains may be native sequence constant domains (e.g. human native sequence constant domains) or amino acid sequence variant thereof. Preferably, the intact antibody has one or more effector functions.

20 "Antibody fragments" comprise a portion of an intact antibody, preferably the antigen binding or variable region of the intact antibody. Examples of antibody fragments include Fab, Fab', F(ab')₂, and Fv fragments; diabodies; linear antibodies (see U.S. Patent No. 5,641,870, Example 2; Zapata et al., Protein Eng. 8(10): 1057-1062 [1995]); single-chain antibody molecules; and multispecific antibodies formed from antibody fragments.

25 Papain digestion of antibodies produces two identical antigen-binding fragments, called "Fab" fragments, and a residual "Fc" fragment, a designation reflecting the ability to crystallize readily. The Fab fragment consists of an entire L chain along with the variable region domain of the H chain (V_H), and the first constant domain of one heavy chain (C_H1). Each Fab fragment is monovalent with respect to antigen binding, i.e., it has a single antigen-binding site. Pepsin treatment of an antibody yields a single large F(ab')₂ fragment 30 which roughly corresponds to two disulfide linked Fab fragments having divalent antigen-binding activity and is still capable of cross-linking antigen. Fab' fragments differ from Fab fragments by having additional few residues at the carboxy terminus of the C_H1 domain including one or more cysteines from the antibody hinge region. Fab'-SH is the designation herein for Fab' in which the cysteine residue(s) of the constant domains bear a free thiol group. F(ab')₂ antibody fragments originally were produced as pairs of Fab' fragments which have 35 hinge cysteines between them. Other chemical couplings of antibody fragments are also known.

The Fc fragment comprises the carboxy-terminal portions of both H chains held together by disulfides.

The effector functions of antibodies are determined by sequences in the Fc region, which region is also the part recognized by Fc receptors (FcR) found on certain types of cells.

"Fv" is the minimum antibody fragment which contains a complete antigen-recognition and -binding site. This fragment consists of a dimer of one heavy- and one light-chain variable region domain in tight, non-covalent association. From the folding of these two domains emanate six hypervariable loops (3 loops each from the H and L chain) that contribute the amino acid residues for antigen binding and confer antigen binding specificity to the antibody. However, even a single variable domain (or half of an Fv comprising only three CDRs specific for an antigen) has the ability to recognize and bind antigen, although at a lower affinity than the entire binding site.

"Single-chain Fv" also abbreviated as "sFv" or "scFv" are antibody fragments that comprise the V_H and V_L antibody domains connected into a single polypeptide chain. Preferably, the sFv polypeptide further comprises a polypeptide linker between the V_H and V_L domains which enables the sFv to form the desired structure for antigen binding. For a review of sFv, see Pluckthun in The Pharmacology of Monoclonal Antibodies, vol. 113, Rosenberg and Moore eds., Springer-Verlag, New York, pp. 269-315 (1994); Borrebaeck 1995, infra.

The term "diabodies" refers to small antibody fragments prepared by constructing sFv fragments (see preceding paragraph) with short linkers (about 5-10 residues) between the V_H and V_L domains such that inter-chain but not intra-chain pairing of the V domains is achieved, resulting in a bivalent fragment, i.e., fragment having two antigen-binding sites. Bispecific diabodies are heterodimers of two "crossover" sFv fragments in which the V_H and V_L domains of the two antibodies are present on different polypeptide chains. Diabodies are described more fully in, for example, EP 404,097; WO 93/11161; and Hollinger et al., Proc. Natl. Acad. Sci. USA, 90:6444-6448 (1993).

"Humanized" forms of non-human (e.g., rodent) antibodies are chimeric antibodies that contain minimal sequence derived from the non-human antibody. For the most part, humanized antibodies are human immunoglobulins (recipient antibody) in which residues from a hypervariable region of the recipient are replaced by residues from a hypervariable region of a non-human species (donor antibody) such as mouse, rat, rabbit or non-human primate having the desired antibody specificity, affinity, and capability. In some instances, framework region (FR) residues of the human immunoglobulin are replaced by corresponding non-human residues. Furthermore, humanized antibodies may comprise residues that are not found in the recipient antibody or in the donor antibody. These modifications are made to further refine antibody performance. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the hypervariable loops correspond to those of a non-human immunoglobulin and all or substantially all of the FRs are those of a human immunoglobulin sequence. The humanized antibody optionally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin. For further details, see Jones et al., Nature 321:522-525 (1986); Riechmann et al., Nature 332:323-329 (1988); and Presta, Curr. Op. Struct. Biol. 2:593-596 (1992).

A "species-dependent antibody," e.g., a mammalian anti-human IgE antibody, is an antibody which

has a stronger binding affinity for an antigen from a first mammalian species than it has for a homologue of that antigen from a second mammalian species. Normally, the species-dependent antibody "bind specifically" to a human antigen (i.e., has a binding affinity (Kd) value of no more than about 1×10^{-7} M, preferably no more than about 1×10^{-8} and most preferably no more than about 1×10^{-9} M) but has a binding affinity for a homologue of the antigen from a second non-human mammalian species which is at least about 50 fold, or at 5 least about 500 fold, or at least about 1000 fold, weaker than its binding affinity for the human antigen. The species-dependent antibody can be of any of the various types of antibodies as defined above, but preferably is a humanized or human antibody.

A "TAT binding oligopeptide" is an oligopeptide that binds, preferably specifically, to a TAT polypeptide as described herein. TAT binding oligopeptides may be chemically synthesized using known 10 oligopeptide synthesis methodology or may be prepared and purified using recombinant technology. TAT binding oligopeptides are usually at least about 5 amino acids in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 15 94, 95, 96, 97, 98, 99, or 100 amino acids in length or more, wherein such oligopeptides that are capable of binding, preferably specifically, to a TAT polypeptide as described herein. TAT binding oligopeptides may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening oligopeptide libraries for oligopeptides that are capable of specifically binding to a polypeptide target are well known in the art (see, e.g., U.S. Patent Nos. 5,556,762, 5,750,373, 4,708,871, 4,833,092, 20 5,223,409, 5,403,484, 5,571,689, 5,663,143; PCT Publication Nos. WO 84/03506 and WO84/03564; Geysen et al., Proc. Natl. Acad. Sci. U.S.A., 81:3998-4002 (1984); Geysen et al., Proc. Natl. Acad. Sci. U.S.A., 82:178-182 (1985); Geysen et al., in Synthetic Peptides as Antigens, 130-149 (1986); Geysen et al., J. Immunol. Meth., 102:259-274 (1987); Schoofs et al., J. Immunol., 140:611-616 (1988), Cwirla, S. E. et al. (1990) Proc. Natl. Acad. Sci. USA, 87:6378; Lowman, H.B. et al. (1991) Biochemistry, 30:10832; Clackson, 25 T. et al. (1991) Nature, 352: 624; Marks, J. D. et al. (1991), J. Mol. Biol., 222:581; Kang, A.S. et al. (1991) Proc. Natl. Acad. Sci. USA, 88:8363, and Smith, G. P. (1991) Current Opin. Biotechnol., 2:668).

A "TAT binding organic molecule" is an organic molecule other than an oligopeptide or antibody as defined herein that binds, preferably specifically, to a TAT polypeptide as described herein. TAT binding organic molecules may be identified and chemically synthesized using known methodology (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585). TAT binding organic molecules are usually less than about 2000 daltons in size, alternatively less than about 1500, 750, 500, 250 or 200 daltons in size, wherein such 5 organic molecules that are capable of binding, preferably specifically, to a TAT polypeptide as described herein may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening organic molecule libraries for molecules that are capable of binding to a polypeptide target are well known in the art (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585).

An antibody, oligopeptide or other organic molecule "which binds" an antigen of interest, e.g. a tumor-associated polypeptide antigen target, is one that binds the antigen with sufficient affinity such that the antibody, oligopeptide or other organic molecule is useful as a diagnostic and/or therapeutic agent in targeting a cell or tissue expressing the antigen, and does not significantly cross-react with other proteins. In such embodiments, the extent of binding of the antibody, oligopeptide or other organic molecule to a "non-target" protein will be less than about 10% of the binding of the antibody, oligopeptide or other organic molecule to its particular target 10 protein as determined by fluorescence activated cell sorting (FACS) analysis or radioimmunoprecipitation (RIA). With regard to the binding of an antibody, oligopeptide or other organic molecule to a target molecule, the term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target means binding that is measurably different from a non-specific interaction. Specific binding can be measured, for example, by determining binding of a molecule compared to binding of a control 15 molecule, which generally is a molecule of similar structure that does not have binding activity. For example, specific binding can be determined by competition with a control molecule that is similar to the target, for example, an excess of non-labeled target. In this case, specific binding is indicated if the binding of the labeled target to a probe is competitively inhibited by excess unlabeled target. The term "specific binding" or "specifically binds to" or is "specific for" a particular polypeptide or an epitope on a particular polypeptide target as used herein can be exhibited, for example, by a molecule having a Kd for the target of at least about 20 10^{-4} M, alternatively at least about 10^{-5} M, alternatively at least about 10^{-6} M, alternatively at least about 10^{-7} M, alternatively at least about 10^{-8} M, alternatively at least about 10^{-9} M, alternatively at least about 10^{-10} M, alternatively at least about 10^{-11} M, alternatively at least about 10^{-12} M, or greater. In one embodiment, the term "specific binding" refers to binding where a molecule binds to a particular polypeptide or epitope on a particular 25 polypeptide without substantially binding to any other polypeptide or polypeptide epitope.

An antibody, oligopeptide or other organic molecule that "inhibits the growth of tumor cells expressing a TAT polypeptide" or a "growth inhibitory" antibody, oligopeptide or other organic molecule is one which results in measurable growth inhibition of cancer cells expressing or overexpressing the appropriate TAT polypeptide. The TAT polypeptide may be a transmembrane polypeptide expressed on the surface of a cancer 30 cell or may be a polypeptide that is produced and secreted by a cancer cell. Preferred growth inhibitory anti-TAT antibodies, oligopeptides or organic molecules inhibit growth of TAT-expressing tumor cells by greater

than 20%, preferably from about 20% to about 50%, and even more preferably, by greater than 50% (e.g., from about 50% to about 100%) as compared to the appropriate control, the control typically being tumor cells not treated with the antibody, oligopeptide or other organic molecule being tested. In one embodiment, growth inhibition can be measured at an antibody concentration of about 0.1 to 30 μ g/ml or about 0.5 nM to 200 nM in cell culture, where the growth inhibition is determined 1-10 days after exposure of the tumor cells to the antibody. Growth inhibition of tumor cells *in vivo* can be determined in various ways such as is described in the Experimental Examples section below. The antibody is growth inhibitory *in vivo* if administration of the anti-TAT antibody at about 1 μ g/kg to about 100 mg/kg body weight results in reduction in tumor size or tumor cell proliferation within about 5 days to 3 months from the first administration of the antibody, preferably within about 5 to 30 days.

An antibody, oligopeptide or other organic molecule which "induces apoptosis" is one which induces programmed cell death as determined by binding of annexin V, fragmentation of DNA, cell shrinkage, dilation of endoplasmic reticulum, cell fragmentation, and/or formation of membrane vesicles (called apoptotic bodies). The cell is usually one which overexpresses a TAT polypeptide. Preferably the cell is a tumor cell, e.g., a prostate, breast, ovarian, stomach, endometrial, lung, kidney, colon, bladder cell. Various methods are available for evaluating the cellular events associated with apoptosis. For example, phosphatidyl serine (PS) translocation can be measured by annexin binding; DNA fragmentation can be evaluated through DNA laddering; and nuclear/chromatin condensation along with DNA fragmentation can be evaluated by any increase in hypodiploid cells. Preferably, the antibody, oligopeptide or other organic molecule which induces apoptosis is one which results in about 2 to 50 fold, preferably about 5 to 50 fold, and most preferably about 10 to 50 fold, induction of annexin binding relative to untreated cell in an annexin binding assay.

Antibody "effector functions" refer to those biological activities attributable to the Fc region (a native sequence Fc region or amino acid sequence variant Fc region) of an antibody, and vary with the antibody isotype. Examples of antibody effector functions include: C1q binding and complement dependent cytotoxicity; Fc receptor binding; antibody-dependent cell-mediated cytotoxicity (ADCC); phagocytosis; down regulation of cell surface receptors (e.g., B cell receptor); and B cell activation.

"Antibody-dependent cell-mediated cytotoxicity" or "ADCC" refers to a form of cytotoxicity in which secreted Ig bound onto Fc receptors (FcRs) present on certain cytotoxic cells (e.g., Natural Killer (NK) cells, neutrophils, and macrophages) enable these cytotoxic effector cells to bind specifically to an antigen-bearing target cell and subsequently kill the target cell with cytotoxins. The antibodies "arm" the cytotoxic cells and are absolutely required for such killing. The primary cells for mediating ADCC, NK cells, express Fc γ RIII only, whereas monocytes express Fc γ RI, Fc γ RII and Fc γ RIII. FcR expression on hematopoietic cells is summarized in Table 3 on page 464 of Ravetch and Kinet, *Annu. Rev. Immunol.* 9:457-92 (1991). To assess ADCC activity of a molecule of interest, an *in vitro* ADCC assay, such as that described in US Patent No. 5,500,362 or 5,821,337 may be performed. Useful effector cells for such assays include peripheral blood mononuclear cells (PBMC) and Natural Killer (NK) cells. Alternatively, or additionally, ADCC activity of the molecule of interest may be assessed *in vivo*, e.g., in a animal model such as that disclosed in Clynes et al.

(USA) 95:652-656 (1998).

"Fc receptor" or "FcR" describes a receptor that binds to the Fc region of an antibody. The preferred FcR is a native sequence human FcR. Moreover, a preferred FcR is one which binds an IgG antibody (a gamma receptor) and includes receptors of the Fc γ RI, Fc γ RII and Fc γ RIII subclasses, including allelic variants and alternatively spliced forms of these receptors. Fc γ RII receptors include Fc γ RIIA (an "activating receptor") and Fc γ RIIB (an "inhibiting receptor"), which have similar amino acid sequences that differ primarily in the cytoplasmic domains thereof. Activating receptor Fc γ RIIA contains an immunoreceptor tyrosine-based activation motif (ITAM) in its cytoplasmic domain. Inhibiting receptor Fc γ RIIB contains an immunoreceptor tyrosine-based inhibition motif (ITIM) in its cytoplasmic domain. (see review M. in Daëron, Annu. Rev. Immunol. 15:203-234 (1997)). FcRs are reviewed in Ravetch and Kinet, Annu. Rev. Immunol. 9:457-492 (1991); Capel et al., Immunomethods 4:25-34 (1994); and de Haas et al., J. Lab. Clin. Med. 126:330-41 (1995). Other FcRs, including those to be identified in the future, are encompassed by the term "FcR" herein. The term also includes the neonatal receptor, FcRn, which is responsible for the transfer of maternal IgGs to the fetus (Guyer et al., J. Immunol. 117:587 (1976) and Kim et al., J. Immunol. 24:249 (1994)).

"Human effector cells" are leukocytes which express one or more FcRs and perform effector functions. Preferably, the cells express at least Fc γ RIII and perform ADCC effector function. Examples of human leukocytes which mediate ADCC include peripheral blood mononuclear cells (PBMC), natural killer (NK) cells, monocytes, cytotoxic T cells and neutrophils; with PBMCs and NK cells being preferred. The effector cells may be isolated from a native source, e.g., from blood.

"Complement dependent cytotoxicity" or "CDC" refers to the lysis of a target cell in the presence of complement. Activation of the classical complement pathway is initiated by the binding of the first component of the complement system (C1q) to antibodies (of the appropriate subclass) which are bound to their cognate antigen. To assess complement activation, a CDC assay, e.g., as described in Gazzano-Santoro et al., J. Immunol. Methods 202:163 (1996), may be performed.

The terms "cancer" and "cancerous" refer to or describe the physiological condition in mammals that is typically characterized by unregulated cell growth. Examples of cancer include, but are not limited to, carcinoma, lymphoma, blastoma, sarcoma, and leukemia or lymphoid malignancies. More particular examples of such cancers include squamous cell cancer (e.g., epithelial squamous cell cancer), lung cancer including small-cell lung cancer, non-small cell lung cancer, adenocarcinoma of the lung and squamous carcinoma of the lung, cancer of the peritoneum, hepatocellular cancer, gastric or stomach cancer including gastrointestinal cancer, pancreatic cancer, glioblastoma, cervical cancer, ovarian cancer, liver cancer, bladder cancer, cancer of the urinary tract, hepatoma, breast cancer, colon cancer, rectal cancer, colorectal cancer, endometrial or uterine carcinoma, salivary gland carcinoma, kidney or renal cancer, prostate cancer, vulval cancer, thyroid cancer, hepatic carcinoma, anal carcinoma, penile carcinoma, melanoma, multiple myeloma and B-cell lymphoma, brain, as well as head and neck cancer, and associated metastases.

The terms "cell proliferative disorder" and "proliferative disorder" refer to disorders that are

associated with some degree of abnormal cell proliferation. In one embodiment, the cell proliferative disorder is cancer.

"Tumor", as used herein, refers to all neoplastic cell growth and proliferation, whether malignant or benign, and all pre-cancerous and cancerous cells and tissues.

An antibody, oligopeptide or other organic molecule which "induces cell death" is one which causes a viable cell to become nonviable. The cell is one which expresses a TAT polypeptide, preferably a cell that overexpresses a TAT polypeptide as compared to a normal cell of the same tissue type. The TAT polypeptide may be a transmembrane polypeptide expressed on the surface of a cancer cell or may be a polypeptide that is produced and secreted by a cancer cell. Preferably, the cell is a cancer cell, e.g., a breast, ovarian, stomach, 5 endometrial, salivary gland, lung, kidney, colon, thyroid, pancreatic or bladder cell. Cell death *in vitro* may be determined in the absence of complement and immune effector cells to distinguish cell death induced by antibody-dependent cell-mediated cytotoxicity (ADCC) or complement dependent cytotoxicity (CDC). Thus, 10 the assay for cell death may be performed using heat inactivated serum (i.e., in the absence of complement) and in the absence of immune effector cells. To determine whether the antibody, oligopeptide or other organic molecule is able to induce cell death, loss of membrane integrity as evaluated by uptake of propidium iodide (PI), trypan blue (see Moore et al. *Cytotechnology* 17:1-11 (1995)) or 7AAD can be assessed relative to 15 untreated cells. Preferred cell death-inducing antibodies, oligopeptides or other organic molecules are those which induce PI uptake in the PI uptake assay in BT474 cells.

A "TAT-expressing cell" is a cell which expresses an endogenous or transfected TAT polypeptide either on the cell surface or in a secreted form. A "TAT-expressing cancer" is a cancer comprising cells that have a TAT polypeptide present on the cell surface or that produce and secrete a TAT polypeptide. A "TAT-expressing cancer" optionally produces sufficient levels of TAT polypeptide on the surface of cells thereof, such that an anti-TAT antibody, oligopeptide or other organic molecule can bind thereto and have a therapeutic effect with respect to the cancer. In another embodiment, a "TAT-expressing cancer" optionally produces and secretes sufficient levels of TAT polypeptide, such that an anti-TAT antibody, oligopeptide or other organic 20 molecule antagonist can bind thereto and have a therapeutic effect with respect to the cancer. With regard to the latter, the antagonist may be an antisense oligonucleotide which reduces, inhibits or prevents production and secretion of the secreted TAT polypeptide by tumor cells. A cancer which "overexpresses" a TAT polypeptide is one which has significantly higher levels of TAT polypeptide at the cell surface thereof, or produces and secretes, compared to a noncancerous cell of the same tissue type. Such overexpression may be caused by gene 25 amplification or by increased transcription or translation. TAT polypeptide overexpression may be determined in a diagnostic or prognostic assay by evaluating increased levels of the TAT protein present on the surface of a cell, or secreted by the cell (e.g., via an immunohistochemistry assay using anti-TAT antibodies prepared against an isolated TAT polypeptide which may be prepared using recombinant DNA technology from an isolated nucleic acid encoding the TAT polypeptide; FACS analysis, etc.). Alternatively, or additionally, one 30 may measure levels of TAT polypeptide-encoding nucleic acid or mRNA in the cell, e.g., via fluorescent *in situ* hybridization using a nucleic acid based probe corresponding to a TAT-encoding nucleic acid or the complement 35

thereof; (FISH; see WO98/45479 published October, 1998), Southern blotting, Northern blotting, or polymerase chain reaction (PCR) techniques, such as real time quantitative PCR (RT-PCR). One may also study TAT polypeptide overexpression by measuring shed antigen in a biological fluid such as serum, e.g., using antibody-based assays (see also, e.g., U.S. Patent No. 4,933,294 issued June 12, 1990; WO91/05264 published April 18, 1991; U.S. Patent 5,401,638 issued March 28, 1995; and Sias et al., *J. Immunol. Methods* 132:73-80 (1990)). Aside from the above assays, various *in vivo* assays are available to the skilled practitioner. For example, one may expose cells within the body of the patient to an antibody which is optionally labeled with a detectable label, e.g., a radioactive isotope, and binding of the antibody to cells in the patient can be evaluated, e.g., by external scanning for radioactivity or by analyzing a biopsy taken from a patient previously exposed to the antibody.

As used herein, the term "immunoadhesin" designates antibody-like molecules which combine the binding specificity of a heterologous protein (an "adhesin") with the effector functions of immunoglobulin constant domains. Structurally, the immunoadhesins comprise a fusion of an amino acid sequence with the desired binding specificity which is other than the antigen recognition and binding site of an antibody (i.e., is "heterologous"), and an immunoglobulin constant domain sequence. The adhesin part of an immunoadhesin molecule typically is a contiguous amino acid sequence comprising at least the binding site of a receptor or a ligand. The immunoglobulin constant domain sequence in the immunoadhesin may be obtained from any immunoglobulin, such as IgG-1, IgG-2, IgG-3, or IgG-4 subtypes, IgA (including IgA-1 and IgA-2), IgE, IgD or IgM.

The word "label" when used herein refers to a detectable compound or composition which is conjugated directly or indirectly to the antibody, oligopeptide or other organic molecule so as to generate a "labeled" antibody, oligopeptide or other organic molecule. The label may be detectable by itself (e.g. radioisotope labels or fluorescent labels) or, in the case of an enzymatic label, may catalyze chemical alteration of a substrate compound or composition which is detectable.

The term "cytotoxic agent" as used herein refers to a substance that inhibits or prevents the function of cells and/or causes destruction of cells. The term is intended to include radioactive isotopes (e.g., ^{211}At , I^{131} , I^{125} , Y^{90} , Re^{186} , Re^{188} , Sm^{153} , Bi^{212} , P^{32} and radioactive isotopes of Lu), chemotherapeutic agents e.g. methotrexate, adriamicin, vinca alkaloids (vincristine, vinblastine, etoposide), doxorubicin, melphalan, mitomycin C, chlorambucil, daunorubicin or other intercalating agents, enzymes and fragments thereof such as nucleolytic enzymes, antibiotics, and toxins such as small molecule toxins or enzymatically active toxins of bacterial, fungal, plant or animal origin, including fragments and/or variants thereof, and the various antitumor or anticancer agents disclosed below. Other cytotoxic agents are described below. A tumoricidal agent causes destruction of tumor cells.

A "growth inhibitory agent" when used herein refers to a compound or composition which inhibits growth of a cell, especially a TAT-expressing cancer cell, either *in vitro* or *in vivo*. Thus, the growth inhibitory agent may be one which significantly reduces the percentage of TAT-expressing cells in S phase. Examples of growth inhibitory agents include agents that block cell cycle progression (at a place other than S phase), such

as agents that induce G1 arrest and M-phase arrest. Classical M-phase blockers include the vincas (vincristine and vinblastine), taxanes, and topoisomerase II inhibitors such as doxorubicin, epirubicin, daunorubicin, etoposide, and bleomycin. Those agents that arrest G1 also spill over into S-phase arrest, for example, DNA alkylating agents such as tamoxifen, prednisone, dacarbazine, mechlorethamine, cisplatin, methotrexate, 5-fluorouracil, and ara-C. Further information can be found in The Molecular Basis of Cancer, Mendelsohn and Israel, eds., Chapter 1, entitled "Cell cycle regulation, oncogenes, and antineoplastic drugs" by Murakami et al. (WB Saunders: Philadelphia, 1995), especially p. 13. The taxanes (paclitaxel and docetaxel) are anticancer drugs both derived from the yew tree. Docetaxel (TAXOTERE®, Rhone-Poulenc Rorer), derived from the European yew, is a semisynthetic analogue of paclitaxel (TAXOL®, Bristol-Myers Squibb). Paclitaxel and docetaxel promote the assembly of microtubules from tubulin dimers and stabilize microtubules by preventing depolymerization, which results in the inhibition of mitosis in cells.

"Doxorubicin" is an anthracycline antibiotic. The full chemical name of doxorubicin is (8S-cis)-10-[(3-amino-2,3,6-trideoxy- α -L-lyxo-hexapyranosyl)oxy]-7,8,9,10-tetrahydro-6,8,11-trihydroxy-8-(hydroxyacetyl)-1-methoxy-5,12-naphthacenedione.

The term "cytokine" is a generic term for proteins released by one cell population which act on another cell as intercellular mediators. Examples of such cytokines are lymphokines, monokines, and traditional polypeptide hormones. Included among the cytokines are growth hormone such as human growth hormone, N-methionyl human growth hormone, and bovine growth hormone; parathyroid hormone; thyroxine; insulin; proinsulin; relaxin; prorelaxin; glycoprotein hormones such as follicle stimulating hormone (FSH), thyroid stimulating hormone (TSH), and luteinizing hormone (LH); hepatic growth factor; fibroblast growth factor; prolactin; placental lactogen; tumor necrosis factor- α and - β ; mullerian-inhibiting substance; mouse gonadotropin-associated peptide; inhibin; activin; vascular endothelial growth factor; integrin; thrombopoietin (TPO); nerve growth factors such as NGF- β ; platelet-growth factor; transforming growth factors (TGFs) such as TGF- α and TGF- β ; insulin-like growth factor-I and -II; erythropoietin (EPO); osteoinductive factors; interferons such as interferon- α , - β , and - γ ; colony stimulating factors (CSFs) such as macrophage-CSF (M-CSF); granulocyte-macrophage-CSF (GM-CSF); and granulocyte-CSF (G-CSF); interleukins (ILs) such as IL-1, IL-1a, IL-2, IL-3, IL-4, IL-5, IL-6, IL-7, IL-8, IL-9, IL-11, IL-12; a tumor necrosis factor such as TNF- α or TNF- β ; and other polypeptide factors including LIF and kit ligand (KL). As used herein, the term cytokine includes proteins from natural sources or from recombinant cell culture and biologically active equivalents of the native sequence cytokines.

30

The term "package insert" is used to refer to instructions customarily included in commercial packages of therapeutic products, that contain information about the indications, usage, dosage, administration, contraindications and/or warnings concerning the use of such therapeutic products.

Table 1

```

/*
*
* C-C increased from 12 to 15
* Z is average of EQ
5   * B is average of ND
* match with stop is _M; stop-stop = 0; J (joker) match = 0
*/
#define _M     -8      /* value of a match with a stop */

10  int      _day[26][26] = {
/*      A B C D E F G H I J K L M N O P Q R S T U V W X Y Z */
/* A */ { 2, 0,-2, 0, 0,-4, 1,-1,-1, 0,-1,-2,-1, 0,_M, 1, 0,-2, 1, 1, 0, 0,-6, 0,-3, 0 },
/* B */ { 0, 3,-4, 3, 2,-5, 0, 1,-2, 0, 0,-3,-2, 2,_M,-1, 1, 0, 0, 0, 0,-2,-5, 0,-3, 1 },
/* C */ { -2,-4,15,-5,-5,-4,-3,-3,-2, 0,-5,-6,-5,-4,_M,-3,-5,-4, 0,-2, 0,-2,-8, 0, 0,-5 },
15  /* D */ { 0, 3,-5, 4, 3,-6, 1, 1,-2, 0, 0,-4,-3, 2,_M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 2 },
/* E */ { 0, 2,-5, 3, 4,-5, 0, 1,-2, 0, 0,-3,-2, 1,_M,-1, 2,-1, 0, 0, 0,-2,-7, 0,-4, 3 },
/* F */ { -4,-5,-4,-6,-5, 9,-5,-2, 1, 0,-5, 2, 0,-4,_M,-5,-5,-4,-3,-3, 0,-1, 0, 0, 7,-5 },
/* G */ { 1, 0,-3, 1, 0,-5, 5,-2,-3, 0,-2,-4,-3, 0,_M,-1,-1,-3, 1, 0, 0,-1,-7, 0,-5, 0 },
/* H */ { -1, 1,-3, 1, 1,-2,-2, 6,-2, 0, 0,-2,-2, 2,_M, 0, 3, 2,-1,-1, 0,-2,-3, 0, 0, 2 },
20  /* I */ { -1,-2,-2,-2,-2, 1,-3,-2, 5, 0,-2, 2, 2,-2,_M,-2,-2,-2,-1, 0, 0, 4,-5, 0,-1,-2 },
/* J */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0 },
/* K */ { -1, 0,-5, 0, 0,-5,-2, 0,-2, 0, 5,-3, 0, 1,_M,-1, 1, 3, 0, 0, 0,-2,-3, 0,-4, 0 },
/* L */ { -2,-3,-6,-4,-3, 2,-4,-2, 2, 0,-3, 6, 4,-3,_M,-3,-2,-3,-3,-1, 0, 2,-2, 0,-1,-2 },
/* M */ { -1,-2,-5,-3,-2, 0,-3,-2, 2, 0, 0, 4, 6,-2,_M,-2,-1, 0,-2,-1, 0, 2,-4, 0,-2,-1 },
25  /* N */ { 0, 0,-2,-4, 2, 1,-4, 0, 2,-2, 0, 1,-3,-2, 2,_M,-1, 1, 0, 1, 0, 0,-2,-4, 0,-2, 1 },
/* O */ { _M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M,_M },
/* P */ { 1,-1,-3,-1,-1,-5,-1, 0,-2, 0,-1,-3,-2,-1,_M, 6, 0, 0, 1, 0, 0,-1,-6, 0,-5, 0 },
/* Q */ { 0, 1,-5, 2, 2,-5,-1, 3,-2, 0, 1,-2,-1, 1,_M, 0, 4, 1,-1,-1, 0,-2,-5, 0,-4, 3 },
/* R */ { -2, 0,-4,-1,-1,-4,-3, 2,-2, 0, 3,-3, 0, 0,_M, 0, 1, 6, 0,-1, 0,-2, 2, 0,-4, 0 },
30  /* S */ { 1, 0, 0, 0, 0,-3, 1,-1,-1, 0, 0,-3,-2, 1,_M, 1,-1, 0, 2, 1, 0,-1,-2, 0,-3, 0 },
/* T */ { 1, 0,-2, 0, 0,-3, 0,-1, 0, 0, 0,-1,-1, 0,_M, 0,-1,-1, 1, 3, 0, 0,-5, 0,-3, 0 },
/* U */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0 },
/* V */ { 0,-2,-2,-2,-2,-1,-1,-2, 4, 0,-2, 2, 2,-2,_M,-1,-2,-2,-1, 0, 0, 4,-6, 0,-2,-2 },
35  /* W */ { -6,-5,-8,-7,-7, 0,-7,-3,-5, 0,-3,-2,-4,-4,_M,-6,-5, 2,-2,-5, 0,-6, 17, 0, 0,-6 },
/* X */ { 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0,_M, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0, 0 },
/* Y */ { -3,-3, 0,-4,-4, 7,-5, 0,-1, 0,-4,-1,-2,-2,_M,-5,-4,-4,-3,-3, 0,-2, 0, 0, 10,-4 },
/* Z */ { 0, 1,-5, 2, 3,-5, 0, 2,-2, 0, 0,-2,-1, 1,_M, 0, 3, 0, 0, 0, 0,-2,-6, 0,-4, 4 }
};

40

```

40

45

50

Table 1 (cont')

```

/*
*/
#include <stdio.h>
#include <ctype.h>
5
#define MAXJMP 16 /* max jumps in a diag */
#define MAXGAP 24 /* don't continue to penalize gaps larger than this */
#define JMPS 1024 /* max jmps in an path */
#define MX 4 /* save if there's at least MX-1 bases since last jmp */
10
#define DMAT 3 /* value of matching bases */
#define DMIS 0 /* penalty for mismatched bases */
#define DINS0 8 /* penalty for a gap */
#define DINS1 1 /* penalty per base */
15
#define PINS0 8 /* penalty for a gap */
#define PINS1 4 /* penalty per residue */

20
struct jmp {
    short n[MAXJMP]; /* size of jmp (neg for delay) */
    unsigned short x[MAXJMP]; /* base no. of jmp in seq x */
    /* limits seq to 2^16 - 1 */
};

25
struct diag {
    int score; /* score at last jmp */
    long offset; /* offset of prev block */
    short ijmp; /* current jmp index */
    struct jmp jp; /* list of jmps */
};

30
struct path {
    int spc; /* number of leading spaces */
    short n[JMPS]; /* size of jmp (gap) */
    int x[JMPS]; /* loc of jmp (last elem before gap) */
};

35
char *ofile; /* output file name */
char *namex[2]; /* seq names: getseqs() */
char *prog; /* prog name for err msgs */
char *seqx[2]; /* seqs: getseqs() */
40
int dmax; /* best diag: nw0 */
int dmax0; /* final diag */
int dna; /* set if dna: main() */
int endgaps; /* set if penalizing end gaps */
int gapx, gapy; /* total gaps in seqs */
45
int len0, len1; /* seq lens */
int ngapx, ngapy; /* total size of gaps */
int smax; /* max score: nw0 */
int *xbm; /* bitmap for matching */
long offset; /* current offset in jmp file */
50
struct diag *dx; /* holds diagonals */
struct path pp[2]; /* holds path for seqs */

char *calloc(), *malloc(), *index(), *strcpy();
char *getseq(), *g_calloc();

```

Table 1 (cont')

```

/* Needleman-Wunsch alignment program
 *
 * usage: progs file1 file2
 *   where file1 and file2 are two dna or two protein sequences.
 *   The sequences can be in upper- or lower-case and may contain ambiguity
 *   Any lines beginning with ';' or '>' or '<' are ignored
 *   Max file length is 65535 (limited by unsigned short x in the jmp struct)
 *   A sequence with 1/3 or more of its elements ACGTU is assumed to be DNA
 *   Output is in the file "align.out"
 *
 * The program may create a tmp file in /tmp to hold info about traceback.
 * Original version developed under BSD 4.3 on a vax 8650
 */
#include "nw.h"
#include "day.h"

static _dbval[26] = {
    1,14,2,13,0,0,4,11,0,0,12,0,3,15,0,0,0,5,6,8,8,7,9,0,10,0
};

static _pbval[26] = {
    1, 2|(1<<('D'-'A'))|(1<<('N'-'A')), 4, 8, 16, 32, 64,
    128, 256, 0xFFFFFFFF, 1<<10, 1<<11, 1<<12, 1<<13, 1<<14,
    1<<15, 1<<16, 1<<17, 1<<18, 1<<19, 1<<20, 1<<21, 1<<22,
    1<<23, 1<<24, 1<<25|(1<<('E'-'A'))|(1<<('Q'-'A'))
};

main(ac, av)
{
    int ac;
    char *av[];
    {
        prog = av[0];
        if (ac != 3) {
            fprintf(stderr, "usage: %s file1 file2\n", prog);
            fprintf(stderr, "where file1 and file2 are two dna or two protein sequences.\n");
            fprintf(stderr, "The sequences can be in upper- or lower-case\n");
            fprintf(stderr, "Any lines beginning with ';' or '<' are ignored\n");
            fprintf(stderr, "Output is in the file \"align.out\"\n");
            exit(1);
        }
        namex[0] = av[1];
        namex[1] = av[2];
        seqx[0] = getseq(namex[0], &len0);
        seqx[1] = getseq(namex[1], &len1);
        xbm = (dna)? _dbval : _pbval;

        endgaps = 0;          /* 1 to penalize endgaps */
        ofile = "align.out";   /* output file */

        nw0;                  /* fill in the matrix, get the possible jmps */
        readjmps0;             /* get the actual jmps */
        print0;                /* print stats, alignment */

        cleanup0;              /* unlink any tmp files */
    }
}

```

Table 1 (cont')

```

/* do the alignment, return best score: main()
 * dna: values in Fitch and Smith, PNAS, 80, 1382-1386, 1983
 * pro: PAM 250 values
 * When scores are equal, we prefer mismatches to any gap, prefer
 5   * a new gap to extending an ongoing gap, and prefer a gap in seqx
 * to a gap in seq y.
 */
nw0
{
10  char      *px, *py;      /* seqs and ptrs */
  int       *ndely, *dely;   /* keep track of dely */
  int       ndelx, delx;    /* keep track of delx */
  int       *tmp;          /* for swapping row0, row1 */
  int       mis;           /* score for each type */
15  int       ins0, ins1;    /* insertion penalties */
  register  id;            /* diagonal index */
  register  ij;            /* jmp index */
  register  *col0, *col1;   /* score for curr, last row */
  register  xx, yy;        /* index into seqs */
20
  dx = (struct diag *)g_malloc("to get diags", len0+len1+1, sizeof(struct diag));
  ndely = (int *)g_malloc("to get ndely", len1+1, sizeof(int));
  dely = (int *)g_malloc("to get dely", len1+1, sizeof(int));
  col0 = (int *)g_malloc("to get col0", len1+1, sizeof(int));
  col1 = (int *)g_malloc("to get col1", len1+1, sizeof(int));
25  ins0 = (dna)? DINS0 : PINS0;
  ins1 = (dna)? DINS1 : PINS1;
  smax = -10000;
  if (endgaps) {
30    for (col0[0] = dely[0] = -ins0, yy = 1; yy <= len1; yy++) {
        col0[yy] = dely[yy] = col0[yy-1] - ins1;
        ndely[yy] = yy;
      }
      col0[0] = 0;      /* Waterman Bull Math Biol 84 */
35  }
  else
    for (yy = 1; yy <= len1; yy++) {
      dely[yy] = -ins0;
    }
  /* fill in match matrix
40  */
  for (px = seqx[0], xx = 1; xx <= len0; px++, xx++) {
    /* initialize first entry in col
     */
    if (endgaps) {
45      if (xx == 1)
        col1[0] = delx = -(ins0+ins1);
      else
        col1[0] = delx = col0[0] - ins1;
      ndelx = xx;
    }
    else {
50      col1[0] = 0;
      delx = -ins0;
      ndelx = 0;
    }
55  }
}

```

Table 1 (cont')

```

...nw

for (py = seqx[1], yy = 1; yy <= len1; py++, yy++) {
    mis = col0[yy-1];
    if (dna)
        mis += (xbm[*px-'A']&xbm[*py-'A'])? DMAT : DMIS;
    else
        mis += _day[*px-'A'][*py-'A'];

    /* update penalty for del in x seq;
     * favor new del over ongong del
     * ignore MAXGAP if weighting endgaps
     */
    if (endgaps || ndely[yy] < MAXGAP) {
        if (col0[yy] - ins0 >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else {
            dely[yy] -= ins1;
            ndely[yy]++;
        }
    } else {
        if (col0[yy] - (ins0+ins1) >= dely[yy]) {
            dely[yy] = col0[yy] - (ins0+ins1);
            ndely[yy] = 1;
        } else
            ndely[yy]++;
    }

    /* update penalty for del in y seq;
     * favor new del over ongong del
     */
    if (endgaps || ndelx < MAXGAP) {
        if (col1[yy-1] - ins0 >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else {
            delx -= ins1;
            ndelx++;
        }
    } else {
        if (col1[yy-1] - (ins0+ins1) >= delx) {
            delx = col1[yy-1] - (ins0+ins1);
            ndelx = 1;
        } else
            ndelx++;
    }

    /* pick the maximum score; we're favoring
     * mis over any del and delx over dely
     */
    id = xx - yy + len1 - 1;
    if (mis >= delx && mis >= dely[yy])
        col1[yy] = mis;
}

```

...nw

Table 1 (cont')

```

else if (delx >= dely[yy]) {
    col1[yy] = delx;
    ij = dx[id].ijmp;
    if (dx[id].jp.n[0] && (!dna || (ndelx >= MAXJMP
5      && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
        dx[id].ijmp++;
        if (++ij >= MAXJMP) {
            writejmps(id);
            ij = dx[id].ijmp = 0;
            dx[id].offset = offset;
            offset += sizeof(struct jmp) + sizeof(offset);
        }
    }
    dx[id].jp.n[ij] = ndelx;
    dx[id].jp.x[ij] = xx;
    dx[id].score = delx;
15
}
else {
    col1[yy] = dely[yy];
    ij = dx[id].ijmp;
    if (dx[id].jp.n[0] && (!dna || (ndely[yy] >= MAXJMP
20      && xx > dx[id].jp.x[ij]+MX) || mis > dx[id].score+DINS0)) {
        dx[id].ijmp++;
        if (++ij >= MAXJMP) {
            writejmps(id);
            ij = dx[id].ijmp = 0;
            dx[id].offset = offset;
            offset += sizeof(struct jmp) + sizeof(offset);
        }
    }
    dx[id].jp.n[ij] = -ndely[yy];
    dx[id].jp.x[ij] = xx;
    dx[id].score = dely[yy];
30
}
if (xx == len0 && yy < len1) {
    /* last col
     */
    if (endgaps)
        col1[yy] -= ins0+ins1*(len1-yy);
    if (col1[yy] > smax) {
        smax = col1[yy];
        dmax = id;
    }
    }
45
}
if (endgaps && xx < len0)
    col1[yy-1] -= ins0+ins1*(len0-xx);
if (col1[yy-1] > smax) {
    smax = col1[yy-1];
    dmax = id;
50
}
tmp = col0; col0 = col1; col1 = tmp;
}
(void) free((char *)ndely);
(void) free((char *)dely);
(void) free((char *)col0);
55
(void) free((char *)col1);
}

```

Table 1 (cont')

```

/*
 *
 * print() -- only routine visible outside this module
 *
5  * static:
 * getmat() -- trace back best path, count matches: print()
 * pr_align0 -- print alignment of described in array p[]: print()
 * dumpblock() -- dump a block of lines with numbers, stars: pr_align0()
 * nums() -- put out a number line: dumpblock()
10 * putline() -- put out a line (name, [num], seq, [num]): dumpblock()
 * stars() -- put a line of stars: dumpblock()
 * stripname() -- strip any path and prefix from a seqname
 */

15 #include "nw.h"

#define SPC      3
#define P_LINE   256      /* maximum output line */
#define P_SPC    3      /* space between name or num and seq */

20 extern  _day[26][26];
int     olen;          /* set output line length */
FILE   *fx;            /* output file */

25 print()
{
    int     lx, ly, firstgap, lastgap; /* overlap */

    if ((fx = fopen(ofile, "w")) == 0) {
30        fprintf(stderr, "%s: can't write %s\n", prog, ofile);
        cleanup(1);
    }
    fprintf(fx, "<first sequence: %s (length = %d)\n", namex[0], len0);
    fprintf(fx, "<second sequence: %s (length = %d)\n", namex[1], len1);
    olen = 60;
    lx = len0;
    ly = len1;
    firstgap = lastgap = 0;
40    if (dmax < len1 - 1) { /* leading gap in x */
        pp[0].spc = firstgap = len1 - dmax - 1;
        ly -= pp[0].spc;
    }
    else if (dmax > len1 - 1) { /* leading gap in y */
        pp[1].spc = firstgap = dmax - (len1 - 1);
        lx -= pp[1].spc;
    }
45    if (dmax0 < len0 - 1) { /* trailing gap in x */
        lastgap = len0 - dmax0 - 1;
        lx -= lastgap;
    }
    else if (dmax0 > len0 - 1) { /* trailing gap in y */
50        lastgap = dmax0 - (len0 - 1);
        ly -= lastgap;
    }
55    getmat(lx, ly, firstgap, lastgap);
    pr_align0();
}

```

Table 1 (cont')

```

/*
 * trace back the best path, count matches
 */
static
5   getmat(lx, ly, firstgap, lastgap)           getmat
      int      lx, ly;                      /* "core" (minus endgaps) */
      int      firstgap, lastgap;          /* leading/trailing overlap */
{
10   int      nm, i0, i1, siz0, siz1;
    char     outx[32];
    double   pct;
    register int n0, n1;
    register char *p0, *p1;
    /* get total matches, score
     */
15   i0 = i1 = siz0 = siz1 = 0;
    p0 = seqx[0] + pp[1].spc;
    p1 = seqx[1] + pp[0].spc;
    n0 = pp[1].spc + 1;
20   n1 = pp[0].spc + 1;
    nm = 0;
    while ( *p0 && *p1 ) {
        if (siz0) {
25         p1++;
         n1++;
         siz0--;
        }
        else if (siz1) {
            p0++;
            n0++;
            siz1--;
        }
        else {
30         if (xbm[*p0-'A']&xbm[*p1-'A'])
            nm++;
            if (n0++ == pp[0].n[i0])
                siz0 = pp[0].n[i0++];
            if (n1++ == pp[1].n[i1])
                siz1 = pp[1].n[i1++];
40         p0++;
         p1++;
        }
    }
45   /* pct homology:
    * if penalizing endgaps, base is the shorter seq
    * else, knock off overhangs and take shorter core
    */
50   if (endgaps)
        lx = (len0 < len1)? len0 : len1;
    else
        lx = (lx < ly)? lx : ly;
    pct = 100.*(double)nm/(double)lx;
    fprintf(fx, "\n");
55   fprintf(fx, "< %d match%s in an overlap of %d: %.2f percent similarity\n",
        nm, (nm == 1)? ":" : "es", lx, pct);

```

Table 1 (cont')

```

fprintf(fx, "<gaps in first sequence: %d", gapx); ...getmat
if (gapx) {
    (void) sprintf(outx, " (%d %s%s)", 5
        ngapx, (dna)? "base":"residue", (ngapx == 1)? ":"s");
    fprintf(fx, "%s", outx);
fprintf(fx, ", gaps in second sequence: %d", gapy);
if (gapy) {
    (void) sprintf(outx, " (%d %s%s)", 10
        ngapy, (dna)? "base":"residue", (ngapy == 1)? ":"s");
    fprintf(fx, "%s", outx);
}
if (dna)
fprintf(fx, 15
    "\n<score: %d (match = %d, mismatch = %d, gap penalty = %d + %d per base)\n",
    smax, DMAT, DMIS, DINS0, DINS1);
else
fprintf(fx, 20
    "\n<score: %d (Dayhoff PAM 250 matrix, gap penalty = %d + %d per residue)\n",
    smax, PINS0, PINS1);
if (endgaps)
fprintf(fx, 25
    "<endgaps penalized. left endgap: %d %s%s, right endgap: %d %s%s\n",
    firstgap, (dma)? "base" : "residue", (firstgap == 1)? ":"s",
    lastgap, (dma)? "base" : "residue", (lastgap == 1)? ":"s");
else
fprintf(fx, "<endgaps not penalized\n");
}

30
static nm; /* matches in core -- for checking */
static lmax; /* lengths of stripped file names */
static ij[2]; /* jmp index for a path */
static nc[2]; /* number at start of current line */
static ni[2]; /* current elem number -- for gapping */
static siz[2];
static char *ps[2]; /* ptr to current element */
35
static char *po[2]; /* ptr to next output char slot */
static char out[2][P_LINE]; /* output line */
static char star[P_LINE]; /* set by stars() */
*/
/* print alignment of described in struct path pp[] */
40
*/
static
pr_align() pr_align
{
    int nn; /* char count */
    int more;
    register i;
45
    for (i = 0, lmax = 0; i < 2; i++) {
        nn = stripname(namex[i]);
        if (nn > lmax)
            lmax = nn;
        nc[i] = 1;
        ni[i] = 1;
        siz[i] = ij[i] = 0;
        ps[i] = seqx[i];
        po[i] = out[i];
50
    }
55
}

```

Table 1 (cont')

```

for (nn = nm = 0, more = 1; more; ) {
    for (i = more = 0; i < 2; i++) {
        /*
         * do we have more of this sequence?
         */
        if (!*ps[i])
            continue;
        more++;
        if (pp[i].spc) { /* leading space */
            *po[i]++ = ' ';
            pp[i].spc--;
        }
        else if (siz[i]) { /* in a gap */
            *po[i]++ = '-';
            siz[i]--;
        }
        else { /* we're putting a seq element */
            *po[i] = *ps[i];
            if (islower(*ps[i]))
                *ps[i] = toupper(*ps[i]);
            po[i]++;
            ps[i]++;
            /*
             * are we at next gap for this seq?
             */
            if (ni[i] == pp[i].x[ij[i]]) {
                /*
                 * we need to merge all gaps
                 * at this location
                 */
                siz[i] = pp[i].n[ij[i]++];
                while (ni[i] == pp[i].x[ij[i]]) {
                    siz[i] += pp[i].n[ij[i]++];
                }
                ni[i]++;
            }
        }
        if (++nn == olen || !more && nn) {
            dumpblock();
            for (i = 0; i < 2; i++)
                po[i] = out[i];
            nn = 0;
        }
    }
}
/* dump a block of lines, including numbers, stars: pr_align()
 */
static
dumpblock()
{
    register i;
    for (i = 0; i < 2; i++)
        *po[i] = '0';
}

```

Table 1 (cont')**...dumpblock**

```

(void) putc('\n', fx);
for (i = 0; i < 2; i++) {
    if (*out[i] && (*out[i] != ' ' || *(po[i]) != ' ')) {
5        if (i == 0)
            nums(i);
        if (i == 0 && *out[1])
            stars0;
        putline(i);
        if (i == 0 && *out[1])
            sprintf(fx, star);
        if (i == 1)
            nums(i);
    }
15}
/*
 * put out a number line: dumpblock()
 */
20 static
    nums(ix)
    int      ix;      /* index in out[] holding seq line */
{
    char      nline[P_LINE];
25    register   i, j;
    register char  *pn, *px, *py;
    for (pn = nline, i = 0; i < lmax+P_SPC; i++, pn++)
        *pn = ' ';
    for (i = nc[ix], py = out[ix]; *py; py++, pn++) {
30        if (*py == ' ' || *py == '-')
            *pn = ' ';
        else {
            if (i%10 == 0 || (i == 1 && nc[ix] != 1)) {
                j = (i < 0)? -i : i;
                for (px = pn; j; j /= 10, px--)
                    *px = j%10 + '0';
                if (i < 0)
                    *px = '-';
            }
40        else
            *pn = ' ';
        i++;
    }
45    }
    *pn = '\0';
    nc[ix] = i;
    for (pn = nline; *pn; pn++)
        (void) putc(*pn, fx);
    (void) putc('\n', fx);
50}
/*
 * put out a line (name, [num], seq, [num]): dumpblock()
 */
55 static
    putline(ix)
    int      ix;
{

```

Table 1 (cont')

```

...putline

5      int      i;
      register char *px;
for (px = namex[ix], i = 0; *px && *px != ':'; px++, i++)
    (void) putc(*px, fx);
for (; i < lmax+P_SPC; i++)
    (void) putc(' ', fx);

10     /* these count from 1:
      * ni[] is current element (from 1)
      * nc[] is number at start of current line
      */
for (px = out[ix]; *px; px++)
    (void) putc(*px&0x7F, fx);
    (void) putc('\n', fx);
}

20     /*
      * put a line of stars (seqs always in out[0], out[1]): dumpblock()
      */
static stars()
25     {
      int      i;
      register char *p0, *p1, cx, *px;
if (!*out[0] || (*out[0] == ' ' && *(po[0]) == ' ') ||
    !*out[1] || (*out[1] == ' ' && *(po[1]) == ' '))
    return;
px = star;
for (i = lmax+P_SPC; i--) 
    *px++ = ' ';
35     for (p0 = out[0], p1 = out[1]; *p0 && *p1; p0++, p1++) {
    if (isalpha(*p0) && isalpha(*p1)) {
        if (xbm[*p0-'A']&xbm[*p1-'A']) {
            cx = '*';
            nm++;
        }
        else if (!dma && _day[*p0-'A'][*p1-'A'] > 0)
            cx = ':';
        else
            cx = ' ';
    }
    else
        cx = ' ';
    *px++ = cx;
}
*px++ = '\n';
*px = '\0';
55     }

```

Table 1 (cont')

```
/*
 * strip path or prefix from pn, return len: pr_align()
 */
static
5    stripname(pn)
        char    *pn;      /* file name (may be path) */
{
    register char    *px, *py;

10   py = 0;
    for (px = pn; *px; px++)
        if (*px == '/')
            py = px + 1;
15   if (py)
        (void) strcpy(pn, py);
    return(strlen(pn));
}
20
```

Table 1 (cont')

```

/*
 * cleanup() -- cleanup any tmp file
 * getseq() -- read in seq, set dna, len, maxlen
 * g_malloc() -- calloc() with error checkin
 5   * readjmps() -- get the good jmps, from tmp file if necessary
 * writejmps() -- write a filled array of jmps to a tmp file: nw()
 */
#include "nw.h"
#include <sys/file.h>

10  char  *jname = "/tmp/homgXXXXXX";           /* tmp file for jmps */
FILE  *fj;
int   cleanup();                                /* cleanup tmp file */
long  lseek();
15  /*
 * remove any tmp file if we blow
 */
cleanup(i)
20  {
    int   i;
    if (fj)
        (void) unlink(jname);
    exit(i);
}
25  /*
 * read, return ptr to seq, set dna, len, maxlen
 * skip lines starting with ';', '<', or '>'
 * seq in upper or lower case
 */
30  char  *
getseq(file, len)
35  {
    char  *file;    /* file name */
    int   *len;    /* seq len */
    {
        char  line[1024], *pseq;
        register char  *px, *py;
        int   natgc, tlen;
        FILE  *fp;
        if ((fp = fopen(file, "r")) == 0) {
            fprintf(stderr, "%s: can't read %s\n", prog, file);
40            exit(1);
        }
        tlen = natgc = 0;
        while (fgets(line, 1024, fp)) {
45            if (*line == ';' || *line == '<' || *line == '>')
                continue;
            for (px = line; *px != '\n'; px++)
                if (isupper(*px) || islower(*px))
                    tlen++;
        }
50            if ((pseq = malloc((unsigned)(tlen+6))) == 0) {
                fprintf(stderr, "%s: malloc() failed to get %d bytes for %s\n", prog, tlen+6, file);
                exit(1);
            }
55            pseq[0] = pseq[1] = pseq[2] = pseq[3] = '\0';

```

Table 1 (cont')

```

...getseq

5      py = pseq + 4;
      *len = tlen;
      rewind(fp);
      while (fgets(line, 1024, fp)) {
          if (*line == ';' || *line == '<' || *line == '>')
              continue;
          for (px = line; *px != '\n'; px++) {
              if (isupper(*px))
                  *py++ = *px;
10      else if (islower(*px))
                  *py++ = toupper(*px);
              if (index("ATGCU", *(py-1)))
                  natgc++;
15      }
      *py++ = '\0';
      *py = '\0';
      (void) fclose(fp);
20      dna = natgc > (tlen/3);
      return(pseq+4);
  }

  char  *
25      g_calloc(msg, nx, sz)
      char    *msg;           /* program, calling routine */
      int     nx, sz;         /* number and size of elements */
  {
      char    *px, *calloc();
      if ((px = calloc((unsigned)nx, (unsigned)sz)) == 0) {
30      if (*msg) {
          fprintf(stderr, "%s: g_calloc() failed %s (n=%d, sz=%d)\n", prog, msg, nx, sz);
          exit(1);
      }
      return(px);
35  }

  /*
40  * get final jmps from dx[] or tmp file, set pp[], reset dmax: main()
  */
45      readjmps0
  {
      int      fd = -1;
      int      siz, i0, i1;
      register i, j, xx;
      if (fj) {
          (void) fclose(fj);
          if ((fd = open(jname, O_RDONLY, 0)) < 0) {
50          fprintf(stderr, "%s: can't open() %s\n", prog, jname);
          cleanup(1);
      }
  }
55      for (i = i0 = i1 = 0, dmax0 = dmax, xx = len0; ; i++) {
          while (1) {
              for (j = dx[dmax].ijmp; j >= 0 && dx[dmax].jp.x[j] >= xx; j--)
                  ;
  }

```

Table 1 (cont')

...readjmps

```

if (j < 0 && dx[dmax].offset && fj) {
    (void) lseek(fd, dx[dmax].offset, 0);
    (void) read(fd, (char *)&dx[dmax].jp, sizeof(struct jmp));
    (void) read(fd, (char *)&dx[dmax].offset, sizeof(dx[dmax].offset));
    dx[dmax].ijmp = MAXJMP-1;
}
else
    break;
if (i >= JMPS) {
    fprintf(stderr, "%s: too many gaps in alignment\n", prog);
    cleanup(1);
}
if (j >= 0) {
    siz = dx[dmax].jp.n[j];
    xx = dx[dmax].jp.x[j];
    dmax += siz;
    if (siz < 0) { /* gap in second seq */
        pp[1].n[i1] = -siz;
        xx += siz;
        /* id = xx - yy + len1 - 1 */
        pp[1].x[i1] = xx - dmax + len1 - 1;
        gapy++;
        ngapy -= siz;
    }
    /* ignore MAXGAP when doing endgaps */
    siz = (siz < MAXGAP || endgaps)? -siz : MAXGAP;
    i1++;
}
else if (siz > 0) { /* gap in first seq */
    pp[0].n[i0] = siz;
    pp[0].x[i0] = xx;
    gapx++;
    ngapx += siz;
}
/* ignore MAXGAP when doing endgaps */
siz = (siz < MAXGAP || endgaps)? siz : MAXGAP;
i0++;
}
}
else
    break;
}
/* reverse the order of jmps */
for (j = 0, i0--; j < i0; j++, i0--) {
    i = pp[0].n[j]; pp[0].n[j] = pp[0].n[i0]; pp[0].n[i0] = i;
    i = pp[0].x[j]; pp[0].x[j] = pp[0].x[i0]; pp[0].x[i0] = i;
}
for (j = 0, i1--; j < i1; j++, i1--) {
    i = pp[1].n[j]; pp[1].n[j] = pp[1].n[i1]; pp[1].n[i1] = i;
    i = pp[1].x[j]; pp[1].x[j] = pp[1].x[i1]; pp[1].x[i1] = i;
}
if (fd >= 0)
    (void) close(fd);
if (fj) {
    (void) unlink(jname);
    fj = 0;
    offset = 0;
}
}

```

Table 1 (cont')

```

/*
 * write a filled jmp struct offset of the prev one (if any): nw()
 */
5   writejmps(ix)
      int      ix;
      {
        char    *mktemp();
10  if (!fj) {
        if (mktemp(jname) < 0) {
          fprintf(stderr, "%s: can't mktemp() %s\n", prog, jname);
          cleanup(1);
        }
15  if ((fj = fopen(jname, "w")) == 0) {
          fprintf(stderr, "%s: can't write %s\n", prog, jname);
          exit(1);
        }
20  (void) fwrite((char *)&dx[ix].jp, sizeof(struct jmp), 1, fj);
      (void) fwrite((char *)&dx[ix].offset, sizeof(dx[ix].offset), 1, fj);
    }

```

Table 2

| | | |
|--------------------|--------------------|---------------------------|
| TAT | XXXXXXXXXXXXXXXXXX | (Length = 15 amino acids) |
| Comparison Protein | XXXXXYYYYYYYYY | (Length = 12 amino acids) |

5 % amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the TAT polypeptide) =

10 5 divided by 15 = 33.3%

Table 3

| | | |
|-----------------------|------------------|---------------------------|
| TAT | XXXXXXXXXXXX | (Length = 10 amino acids) |
| 15 Comparison Protein | XXXXXYYYYYYYZZYZ | (Length = 15 amino acids) |

% amino acid sequence identity =

(the number of identically matching amino acid residues between the two polypeptide sequences as determined by ALIGN-2) divided by (the total number of amino acid residues of the TAT polypeptide) =

20 5 divided by 10 = 50%

Table 4

| | | |
|----------------|-----------------|---------------------------|
| 25 TAT-DNA | NNNNNNNNNNNNNN | (Length = 14 nucleotides) |
| Comparison DNA | NNNNNNNLLLLLLLL | (Length = 16 nucleotides) |

% nucleic acid sequence identity =

30 (the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the TAT-DNA nucleic acid sequence) =
6 divided by 14 = 42.9%

Table 5

| | | |
|----------------|--------------|---------------------------|
| TAT-DNA | NNNNNNNNNNNN | (Length = 12 nucleotides) |
| Comparison DNA | NNNNLLLLVV | (Length = 9 nucleotides) |

5 % nucleic acid sequence identity =

(the number of identically matching nucleotides between the two nucleic acid sequences as determined by ALIGN-2) divided by (the total number of nucleotides of the TAT-DNA nucleic acid sequence) =

10 4 divided by 12 = 33.3%

II. Compositions and Methods of the Invention

A. Anti-TAT Antibodies

15 In one embodiment, the present invention provides anti-TAT antibodies which may find use herein as therapeutic and/or diagnostic agents. Exemplary antibodies include polyclonal, monoclonal, humanized, bispecific, and heteroconjugate antibodies.

1. Polyclonal Antibodies

20 Polyclonal antibodies are preferably raised in animals by multiple subcutaneous (sc) or intraperitoneal (ip) injections of the relevant antigen and an adjuvant. It may be useful to conjugate the relevant antigen (especially when synthetic peptides are used) to a protein that is immunogenic in the species to be immunized. For example, the antigen can be conjugated to keyhole limpet hemocyanin (KLH), serum albumin, bovine thyroglobulin, or soybean trypsin inhibitor, using a bifunctional or derivatizing agent, e.g., maleimidobenzoyl sulfosuccinimide ester (conjugation through cysteine residues), N-hydroxysuccinimide (through lysine residues), glutaraldehyde, succinic anhydride, SOCl_2 , or $\text{R}^1\text{N}=\text{C}=\text{NR}$, where R and R^1 are different alkyl groups.

25 Animals are immunized against the antigen, immunogenic conjugates, or derivatives by combining, e.g., 100 μg or 5 μg of the protein or conjugate (for rabbits or mice, respectively) with 3 volumes of Freund's complete adjuvant and injecting the solution intradermally at multiple sites. One month later, the animals are boosted with 1/5 to 1/10 the original amount of peptide or conjugate in Freund's complete adjuvant by subcutaneous injection at multiple sites. Seven to 14 days later, the animals are bled and the serum is assayed for antibody titer. Animals are boosted until the titer plateaus. Conjugates also can be made in recombinant cell culture as protein fusions. Also, aggregating agents such as alum are suitably used to enhance the immune response.

30 2. Monoclonal Antibodies

35 Monoclonal antibodies may be made using the hybridoma method first described by Kohler et al., Nature, 256:495 (1975), or may be made by recombinant DNA methods (U.S. Patent No. 4,816,567).

In the hybridoma method, a mouse or other appropriate host animal, such as a hamster, is immunized

as described above to elicit lymphocytes that produce or are capable of producing antibodies that will specifically bind to the protein used for immunization. Alternatively, lymphocytes may be immunized *in vitro*. After immunization, lymphocytes are isolated and then fused with a myeloma cell line using a suitable fusing agent, such as polyethylene glycol, to form a hybridoma cell (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)).

5 The hybridoma cells thus prepared are seeded and grown in a suitable culture medium which medium preferably contains one or more substances that inhibit the growth or survival of the unfused, parental myeloma cells (also referred to as fusion partner). For example, if the parental myeloma cells lack the enzyme hypoxanthine guanine phosphoribosyl transferase (HGPRT or HPRT), the selective culture medium for the hybridomas typically will include hypoxanthine, aminopterin, and thymidine (HAT medium), which substances prevent the growth of HGPRT-deficient cells.

10 Preferred fusion partner myeloma cells are those that fuse efficiently, support stable high-level production of antibody by the selected antibody-producing cells, and are sensitive to a selective medium that selects against the unfused parental cells. Preferred myeloma cell lines are murine myeloma lines, such as those derived from MOPC-21 and MPC-11 mouse tumors available from the Salk Institute Cell Distribution Center, San Diego, California USA, and SP-2 and derivatives e.g., X63-Ag8-653 cells available from the American 15 Type Culture Collection, Manassas, Virginia, USA. Human myeloma and mouse-human heteromyeloma cell lines also have been described for the production of human monoclonal antibodies (Kozbor, J. Immunol., 133:3001 (1984); and Brodeur et al., Monoclonal Antibody Production Techniques and Applications, pp. 51-63 (Marcel Dekker, Inc., New York, 1987)).

20 Culture medium in which hybridoma cells are growing is assayed for production of monoclonal antibodies directed against the antigen. Preferably, the binding specificity of monoclonal antibodies produced by hybridoma cells is determined by immunoprecipitation or by an *in vitro* binding assay, such as radioimmunoassay (RIA) or enzyme-linked immunosorbent assay (ELISA).

25 The binding affinity of the monoclonal antibody can, for example, be determined by the Scatchard analysis described in Munson et al., Anal. Biochem., 107:220 (1980).

Once hybridoma cells that produce antibodies of the desired specificity, affinity, and/or activity are identified, the clones may be subcloned by limiting dilution procedures and grown by standard methods (Goding, Monoclonal Antibodies: Principles and Practice, pp.59-103 (Academic Press, 1986)). Suitable culture media for this purpose include, for example, D-MEM or RPMI-1640 medium. In addition, the hybridoma cells may 30 be grown *in vivo* as ascites tumors in an animal e.g., by i.p. injection of the cells into mice.

The monoclonal antibodies secreted by the subclones are suitably separated from the culture medium, ascites fluid, or serum by conventional antibody purification procedures such as, for example, affinity chromatography (e.g., using protein A or protein G-Sepharose) or ion-exchange chromatography, hydroxylapatite chromatography, gel electrophoresis, dialysis, etc.

35 DNA encoding the monoclonal antibodies is readily isolated and sequenced using conventional procedures (e.g., by using oligonucleotide probes that are capable of binding specifically to genes encoding the

heavy and light chains of murine antibodies). The hybridoma cells serve as a preferred source of such DNA. Once isolated, the DNA may be placed into expression vectors, which are then transfected into host cells such as *E. coli* cells, simian COS cells, Chinese Hamster Ovary (CHO) cells, or myeloma cells that do not otherwise produce antibody protein, to obtain the synthesis of monoclonal antibodies in the recombinant host cells. Review articles on recombinant expression in bacteria of DNA encoding the antibody include Skerra et al., *Curr. Opinion in Immunol.*, 5:256-262 (1993) and Plückthun, *Immunol. Revs.* 130:151-188 (1992).

5 In a further embodiment, monoclonal antibodies or antibody fragments can be isolated from antibody phage libraries generated using the techniques described in McCafferty et al., *Nature*, 348:552-554 (1990). Clackson et al., *Nature*, 352:624-628 (1991) and Marks et al., *J. Mol. Biol.*, 222:581-597 (1991) describe the isolation of murine and human antibodies, respectively, using phage libraries. Subsequent publications describe 10 the production of high affinity (nM range) human antibodies by chain shuffling (Marks et al., *Bio/Technology*, 10:779-783 (1992)), as well as combinatorial infection and *in vivo* recombination as a strategy for constructing very large phage libraries (Waterhouse et al., *Nuc. Acids. Res.* 21:2265-2266 (1993)). Thus, these techniques are viable alternatives to traditional monoclonal antibody hybridoma techniques for isolation of monoclonal antibodies.

15 The DNA that encodes the antibody may be modified to produce chimeric or fusion antibody polypeptides, for example, by substituting human heavy chain and light chain constant domain (C_H and C_L) sequences for the homologous murine sequences (U.S. Patent No. 4,816,567; and Morrison, et al., *Proc. Natl. Acad. Sci. USA*, 81:6851 (1984)), or by fusing the immunoglobulin coding sequence with all or part of the coding sequence for a non-immunoglobulin polypeptide (heterologous polypeptide). The non-immunoglobulin 20 polypeptide sequences can substitute for the constant domains of an antibody, or they are substituted for the variable domains of one antigen-combining site of an antibody to create a chimeric bivalent antibody comprising one antigen-combining site having specificity for an antigen and another antigen-combining site having specificity for a different antigen.

3. Human and Humanized Antibodies

25 The anti-TAT antibodies of the invention may further comprise humanized antibodies or human antibodies. Humanized forms of non-human (e.g., murine) antibodies are chimeric immunoglobulins, immunoglobulin chains or fragments thereof (such as Fv, Fab, Fab', F(ab')₂ or other antigen-binding subsequences of antibodies) which contain minimal sequence derived from non-human immunoglobulin. Humanized antibodies include human immunoglobulins (recipient antibody) in which residues from a 30 complementary determining region (CDR) of the recipient are replaced by residues from a CDR of a non-human species (donor antibody) such as mouse, rat or rabbit having the desired specificity, affinity and capacity. In some instances, Fv framework residues of the human immunoglobulin are replaced by corresponding non-human residues. Humanized antibodies may also comprise residues which are found neither in the recipient antibody nor in the imported CDR or framework sequences. In general, the humanized antibody will comprise substantially all of at least one, and typically two, variable domains, in which all or substantially all of the CDR regions correspond to those of a non-human immunoglobulin and all or substantially all of the FR regions are 35

those of a human immunoglobulin consensus sequence. The humanized antibody optimally also will comprise at least a portion of an immunoglobulin constant region (Fc), typically that of a human immunoglobulin [Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-329 (1988); and Presta, *Curr. Op. Struct. Biol.*, 2:593-596 (1992)].

Methods for humanizing non-human antibodies are well known in the art. Generally, a humanized antibody has one or more amino acid residues introduced into it from a source which is non-human. These non-human amino acid residues are often referred to as "import" residues, which are typically taken from an "import" variable domain. Humanization can be essentially performed following the method of Winter and co-workers [Jones et al., *Nature*, 321:522-525 (1986); Riechmann et al., *Nature*, 332:323-327 (1988); Verhoeyen et al., *Science*, 239:1534-1536 (1988)], by substituting rodent CDRs or CDR sequences for the corresponding sequences of a human antibody. Accordingly, such "humanized" antibodies are chimeric antibodies (U.S. Patent No. 4,816,567), wherein substantially less than an intact human variable domain has been substituted by the corresponding sequence from a non-human species. In practice, humanized antibodies are typically human antibodies in which some CDR residues and possibly some FR residues are substituted by residues from analogous sites in rodent antibodies.

The choice of human variable domains, both light and heavy, to be used in making the humanized antibodies is very important to reduce antigenicity and HAMA response (human anti-mouse antibody) when the antibody is intended for human therapeutic use. According to the so-called "best-fit" method, the sequence of the variable domain of a rodent antibody is screened against the entire library of known human variable domain sequences. The human V domain sequence which is closest to that of the rodent is identified and the human framework region (FR) within it accepted for the humanized antibody (Sims et al., *J. Immunol.* 151:2296 (1993); Chothia et al., *J. Mol. Biol.*, 196:901 (1987)). Another method uses a particular framework region derived from the consensus sequence of all human antibodies of a particular subgroup of light or heavy chains. The same framework may be used for several different humanized antibodies (Carter et al., *Proc. Natl. Acad. Sci. USA*, 89:4285 (1992); Presta et al., *J. Immunol.* 151:2623 (1993)).

It is further important that antibodies be humanized with retention of high binding affinity for the antigen and other favorable biological properties. To achieve this goal, according to a preferred method, humanized antibodies are prepared by a process of analysis of the parental sequences and various conceptual humanized products using three-dimensional models of the parental and humanized sequences. Three-dimensional immunoglobulin models are commonly available and are familiar to those skilled in the art. Computer programs are available which illustrate and display probable three-dimensional conformational structures of selected candidate immunoglobulin sequences. Inspection of these displays permits analysis of the likely role of the residues in the functioning of the candidate immunoglobulin sequence, i.e., the analysis of residues that influence the ability of the candidate immunoglobulin to bind its antigen. In this way, FR residues can be selected and combined from the recipient and import sequences so that the desired antibody characteristic, such as increased affinity for the target antigen(s), is achieved. In general, the hypervariable region residues are directly and most substantially involved in influencing antigen binding.

Various forms of a humanized anti-TAT antibody are contemplated. For example, the humanized antibody may be an antibody fragment, such as a Fab, which is optionally conjugated with one or more cytotoxic agent(s) in order to generate an immunoconjugate. Alternatively, the humanized antibody may be an intact antibody, such as an intact IgG1 antibody.

As an alternative to humanization, human antibodies can be generated. For example, it is now possible to produce transgenic animals (e.g., mice) that are capable, upon immunization, of producing a full repertoire of human antibodies in the absence of endogenous immunoglobulin production. For example, it has been described that the homozygous deletion of the antibody heavy-chain joining region (J_H) gene in chimeric and germ-line mutant mice results in complete inhibition of endogenous antibody production. Transfer of the human germ-line immunoglobulin gene array into such germ-line mutant mice will result in the production of human antibodies upon antigen challenge. See, e.g., Jakobovits et al., Proc. Natl. Acad. Sci. USA, 90:2551 (1993); Jakobovits et al., Nature, 362:255-258 (1993); Bruggemann et al., Year in Immuno. 7:33 (1993); U.S. Patent Nos. 5,545,806, 5,569,825, 5,591,669 (all of GenPharm); 5,545,807; and WO 97/17852.

Alternatively, phage display technology (McCafferty et al., Nature 348:552-553 [1990]) can be used to produce human antibodies and antibody fragments *in vitro*, from immunoglobulin variable (V) domain gene repertoires from unimmunized donors. According to this technique, antibody V domain genes are cloned in-frame into either a major or minor coat protein gene of a filamentous bacteriophage, such as M13 or fd, and displayed as functional antibody fragments on the surface of the phage particle. Because the filamentous particle contains a single-stranded DNA copy of the phage genome, selections based on the functional properties of the antibody also result in selection of the gene encoding the antibody exhibiting those properties. Thus, the phage mimics some of the properties of the B-cell. Phage display can be performed in a variety of formats, reviewed in, e.g., Johnson, Kevin S. and Chiswell, David J., Current Opinion in Structural Biology 3:564-571 (1993). Several sources of V-gene segments can be used for phage display. Clackson et al., Nature, 352:624-628 (1991) isolated a diverse array of anti-oxazolone antibodies from a small random combinatorial library of V genes derived from the spleens of immunized mice. A repertoire of V genes from unimmunized human donors can be constructed and antibodies to a diverse array of antigens (including self-antigens) can be isolated essentially following the techniques described by Marks et al., J. Mol. Biol. 222:581-597 (1991), or Griffith et al., EMBO J. 12:725-734 (1993). See, also, U.S. Patent Nos. 5,565,332 and 5,573,905.

As discussed above, human antibodies may also be generated by *in vitro* activated B cells (see U.S. Patents 5,567,610 and 5,229,275).

30 4. Antibody fragments

In certain circumstances there are advantages of using antibody fragments, rather than whole antibodies. The smaller size of the fragments allows for rapid clearance, and may lead to improved access to solid tumors.

35 Various techniques have been developed for the production of antibody fragments. Traditionally, these fragments were derived via proteolytic digestion of intact antibodies (see, e.g., Morimoto et al., Journal of Biochemical and Biophysical Methods 24:107-117 (1992); and Brennan et al., Science, 229:81 (1985)).

However, these fragments can now be produced directly by recombinant host cells. Fab, Fv and ScFv antibody fragments can all be expressed in and secreted from *E. coli*, thus allowing the facile production of large amounts of these fragments. Antibody fragments can be isolated from the antibody phage libraries discussed above. Alternatively, Fab'-SH fragments can be directly recovered from *E. coli* and chemically coupled to form F(ab')₂ fragments (Carter et al., *Bio/Technology* 10:163-167 (1992)). According to another approach, F(ab')₂ fragments can be isolated directly from recombinant host cell culture. Fab and F(ab')₂ fragment with increased in vivo half-life comprising a salvage receptor binding epitope residues are described in U.S. Patent No. 5,869,046. Other techniques for the production of antibody fragments will be apparent to the skilled practitioner. In other embodiments, the antibody of choice is a single chain Fv fragment (scFv). See WO 93/16185; U.S. Patent No. 5,571,894; and U.S. Patent No. 5,587,458. Fv and sFv are the only species with intact combining sites that are devoid of constant regions; thus, they are suitable for reduced nonspecific binding during in vivo use. sFv fusion proteins may be constructed to yield fusion of an effector protein at either the amino or the carboxy terminus of an sFv. See *Antibody Engineering*, ed. Borrebaeck, supra. The antibody fragment may also be a "linear antibody", e.g., as described in U.S. Patent 5,641,870 for example. Such linear antibody fragments may be monospecific or bispecific.

15. Bispecific Antibodies

Bispecific antibodies are antibodies that have binding specificities for at least two different epitopes. Exemplary bispecific antibodies may bind to two different epitopes of a TAT protein as described herein. Other such antibodies may combine a TAT binding site with a binding site for another protein. Alternatively, an anti-TAT arm may be combined with an arm which binds to a triggering molecule on a leukocyte such as a T-cell receptor molecule (e.g. CD3), or Fc receptors for IgG (Fc γ R), such as Fc γ RI (CD64), Fc γ RII (CD32) and Fc γ RIII (CD16), so as to focus and localize cellular defense mechanisms to the TAT-expressing cell. Bispecific antibodies may also be used to localize cytotoxic agents to cells which express TAT. These antibodies possess a TAT-binding arm and an arm which binds the cytotoxic agent (e.g., saporin, anti-interferon- α , vinca alkaloid, ricin A chain, methotrexate or radioactive isotope hapten). Bispecific antibodies can be prepared as full length antibodies or antibody fragments (e.g., F(ab')₂ bispecific antibodies).

WO 96/16673 describes a bispecific anti-ErbB2/anti-Fc γ RIII antibody and U.S. Patent No. 5,837,234 discloses a bispecific anti-ErbB2/anti-Fc γ RI antibody. A bispecific anti-ErbB2/Fc α antibody is shown in WO98/02463. U.S. Patent No. 5,821,337 teaches a bispecific anti-ErbB2/anti-CD3 antibody.

Methods for making bispecific antibodies are known in the art. Traditional production of full length bispecific antibodies is based on the co-expression of two immunoglobulin heavy chain-light chain pairs, where the two chains have different specificities (Millstein et al., *Nature* 305:537-539 (1983)). Because of the random assortment of immunoglobulin heavy and light chains, these hybridomas (quadromas) produce a potential mixture of 10 different antibody molecules, of which only one has the correct bispecific structure. Purification of the correct molecule, which is usually done by affinity chromatography steps, is rather cumbersome, and the product yields are low. Similar procedures are disclosed in WO 93/08829, and in Traunecker et al., *EMBO J.* 10:3655-3659 (1991).

According to a different approach, antibody variable domains with the desired binding specificities (antibody-antigen combining sites) are fused to immunoglobulin constant domain sequences. Preferably, the fusion is with an Ig heavy chain constant domain, comprising at least part of the hinge, C_H2, and C_H3 regions. It is preferred to have the first heavy-chain constant region (C_H1) containing the site necessary for light chain bonding, present in at least one of the fusions. DNAs encoding the immunoglobulin heavy chain fusions and, if desired, the immunoglobulin light chain, are inserted into separate expression vectors, and are co-transfected into a suitable host cell. This provides for greater flexibility in adjusting the mutual proportions of the three polypeptide fragments in embodiments when unequal ratios of the three polypeptide chains used in the construction provide the optimum yield of the desired bispecific antibody. It is, however, possible to insert the coding sequences for two or all three polypeptide chains into a single expression vector when the expression of at least two polypeptide chains in equal ratios results in high yields or when the ratios have no significant affect on the yield of the desired chain combination.

In a preferred embodiment of this approach, the bispecific antibodies are composed of a hybrid immunoglobulin heavy chain with a first binding specificity in one arm, and a hybrid immunoglobulin heavy chain-light chain pair (providing a second binding specificity) in the other arm. It was found that this asymmetric structure facilitates the separation of the desired bispecific compound from unwanted immunoglobulin chain combinations, as the presence of an immunoglobulin light chain in only one half of the bispecific molecule provides for a facile way of separation. This approach is disclosed in WO 94/04690. For further details of generating bispecific antibodies see, for example, Suresh et al., Methods in Enzymology 121:210 (1986).

According to another approach described in U.S. Patent No. 5,731,168, the interface between a pair of antibody molecules can be engineered to maximize the percentage of heterodimers which are recovered from recombinant cell culture. The preferred interface comprises at least a part of the C_H3 domain. In this method, one or more small amino acid side chains from the interface of the first antibody molecule are replaced with larger side chains (e.g., tyrosine or tryptophan). Compensatory "cavities" of identical or similar size to the large side chain(s) are created on the interface of the second antibody molecule by replacing large amino acid side chains with smaller ones (e.g., alanine or threonine). This provides a mechanism for increasing the yield of the heterodimer over other unwanted end-products such as homodimers.

Bispecific antibodies include cross-linked or "heteroconjugate" antibodies. For example, one of the antibodies in the heteroconjugate can be coupled to avidin, the other to biotin. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells (U.S. Patent No. 4,676,980), and for treatment of HIV infection (WO 91/00360, WO 92/200373, and EP 03089). Heteroconjugate antibodies may be made using any convenient cross-linking methods. Suitable cross-linking agents are well known in the art, and are disclosed in U.S. Patent No. 4,676,980, along with a number of cross-linking techniques.

Techniques for generating bispecific antibodies from antibody fragments have also been described in the literature. For example, bispecific antibodies can be prepared using chemical linkage. Brennan et al., Science 229:81 (1985) describe a procedure wherein intact antibodies are proteolytically cleaved to generate

5

F(ab')₂ fragments. These fragments are reduced in the presence of the dithiol complexing agent, sodium arsenite, to stabilize vicinal dithiols and prevent intermolecular disulfide formation. The Fab' fragments generated are then converted to thionitrobenzoate (TNB) derivatives. One of the Fab'-TNB derivatives is then reconverted to the Fab'-thiol by reduction with mercaptoethylamine and is mixed with an equimolar amount of the other Fab'-TNB derivative to form the bispecific antibody. The bispecific antibodies produced can be used as agents for the selective immobilization of enzymes.

10

Recent progress has facilitated the direct recovery of Fab'-SH fragments from *E. coli*, which can be chemically coupled to form bispecific antibodies. Shalaby et al., *J. Exp. Med.* 175: 217-225 (1992) describe the production of a fully humanized bispecific antibody F(ab')₂ molecule. Each Fab' fragment was separately secreted from *E. coli* and subjected to directed chemical coupling *in vitro* to form the bispecific antibody. The bispecific antibody thus formed was able to bind to cells overexpressing the ErbB2 receptor and normal human T cells, as well as trigger the lytic activity of human cytotoxic lymphocytes against human breast tumor targets.

15

Various techniques for making and isolating bispecific antibody fragments directly from recombinant cell culture have also been described. For example, bispecific antibodies have been produced using leucine zippers. Kostelny et al., *J. Immunol.* 148(5):1547-1553 (1992). The leucine zipper peptides from the Fos and Jun proteins were linked to the Fab' portions of two different antibodies by gene fusion. The antibody homodimers were reduced at the hinge region to form monomers and then re-oxidized to form the antibody heterodimers. This method can also be utilized for the production of antibody homodimers. The "diabody" technology described by Hollinger et al., *Proc. Natl. Acad. Sci. USA* 90:6444-6448 (1993) has provided an alternative mechanism for making bispecific antibody fragments. The fragments comprise a V_H connected to a V_L by a linker which is too short to allow pairing between the two domains on the same chain. Accordingly, the V_H and V_L domains of one fragment are forced to pair with the complementary V_L and V_H domains of another fragment, thereby forming two antigen-binding sites. Another strategy for making bispecific antibody fragments by the use of single-chain Fv (sFv) dimers has also been reported. See Gruber et al., *J. Immunol.* 152:5368 (1994).

20

Antibodies with more than two valencies are contemplated. For example, trispecific antibodies can be prepared. Tutt et al., *J. Immunol.* 147:60 (1991).

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6. Heteroconjugate Antibodies

Heteroconjugate antibodies are also within the scope of the present invention. Heteroconjugate antibodies are composed of two covalently joined antibodies. Such antibodies have, for example, been proposed to target immune system cells to unwanted cells [U.S. Patent No. 4,676,980], and for treatment of HIV infection [WO 91/00360; WO 92/200373; EP 03089]. It is contemplated that the antibodies may be prepared *in vitro* using known methods in synthetic protein chemistry, including those involving crosslinking agents. For example, immunotoxins may be constructed using a disulfide exchange reaction or by forming a thioether bond. Examples of suitable reagents for this purpose include iminothiolate and methyl-4-mercaptoputyrimidate and those disclosed, for example, in U.S. Patent No. 4,676,980.

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7. Multivalent Antibodies

A multivalent antibody may be internalized (and/or catabolized) faster than a bivalent antibody by a cell expressing an antigen to which the antibodies bind. The antibodies of the present invention can be multivalent antibodies (which are other than of the IgM class) with three or more antigen binding sites (e.g. tetravalent antibodies), which can be readily produced by recombinant expression of nucleic acid encoding the polypeptide chains of the antibody. The multivalent antibody can comprise a dimerization domain and three or 5 more antigen binding sites. The preferred dimerization domain comprises (or consists of) an Fc region or a hinge region. In this scenario, the antibody will comprise an Fc region and three or more antigen binding sites amino-terminal to the Fc region. The preferred multivalent antibody herein comprises (or consists of) three to about eight, but preferably four, antigen binding sites. The multivalent antibody comprises at least one 10 polypeptide chain (and preferably two polypeptide chains), wherein the polypeptide chain(s) comprise two or more variable domains. For instance, the polypeptide chain(s) may comprise $VD1-(X1)_n-VD2-(X2)_n-Fc$, wherein VD1 is a first variable domain, VD2 is a second variable domain, Fc is one polypeptide chain of an Fc region, X1 and X2 represent an amino acid or polypeptide, and n is 0 or 1. For instance, the polypeptide chain(s) may comprise: VH-CH1-flexible linker-VH-CH1-Fc region chain; or VH-CH1-VH-CH1-Fc region chain. The multivalent antibody herein preferably further comprises at least two (and preferably four) light chain 15 variable domain polypeptides. The multivalent antibody herein may, for instance, comprise from about two to about eight light chain variable domain polypeptides. The light chain variable domain polypeptides contemplated here comprise a light chain variable domain and, optionally, further comprise a CL domain.

8. Effector Function Engineering

It may be desirable to modify the antibody of the invention with respect to effector function, e.g., so 20 as to enhance antigen-dependent cell-mediated cytotoxicity (ADCC) and/or complement dependent cytotoxicity (CDC) of the antibody. This may be achieved by introducing one or more amino acid substitutions in an Fc region of the antibody. Alternatively or additionally, cysteine residue(s) may be introduced in the Fc region, thereby allowing interchain disulfide bond formation in this region. The homodimeric antibody thus generated 25 may have improved internalization capability and/or increased complement-mediated cell killing and antibody-dependent cellular cytotoxicity (ADCC). See Caron et al., *J. Exp Med.* 176:1191-1195 (1992) and Shope, B. *J. Immunol.* 148:2918-2922 (1992). Homodimeric antibodies with enhanced anti-tumor activity may also be prepared using heterobifunctional cross-linkers as described in Wolff et al., *Cancer Research* 53:2560-2565 (1993). Alternatively, an antibody can be engineered which has dual Fc regions and may thereby have enhanced complement lysis and ADCC capabilities. See Stevenson et al., *Anti-Cancer Drug Design* 3:219-230 (1989).

30 To increase the serum half life of the antibody, one may incorporate a salvage receptor binding epitope into the antibody (especially an antibody fragment) as described in U.S. Patent 5,739,277, for example. As used herein, the term "salvage receptor binding epitope" refers to an epitope of the Fc region of an IgG molecule (e.g., IgG₁, IgG₂, IgG₃, or IgG₄) that is responsible for increasing the *in vivo* serum half-life of the IgG molecule.

35 9. Immunoconjugates

The invention also pertains to immunoconjugates comprising an antibody conjugated to a cytotoxic

agent such as a chemotherapeutic agent, a growth inhibitory agent, a toxin (e.g., an enzymatically active toxin of bacterial, fungal, plant, or animal origin, or fragments thereof), or a radioactive isotope (i.e., a radioconjugate).

Chemotherapeutic agents useful in the generation of such immunoconjugates have been described above. Enzymatically active toxins and fragments thereof that can be used include diphtheria A chain, 5 nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin, and the trichothecenes. A variety of radionuclides are available for the production of radioconjugated antibodies. Examples include ^{212}Bi , ^{131}I , 10 ^{113}In , ^{90}Y , and ^{186}Re . Conjugates of the antibody and cytotoxic agent are made using a variety of bifunctional protein-coupling agents such as N-succinimidyl-3-(2-pyridyldithiol) propionate (SPDP), iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta *et al.*, *Science*, 238: 1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026.

Conjugates of an antibody and one or more small molecule toxins, such as a calicheamicin, 20 maytansinoids, a trichothene, and CC1065, and the derivatives of these toxins that have toxin activity, are also contemplated herein.

Maytansine and maytansinoids

In one preferred embodiment, an anti-TAT antibody (full length or fragments) of the invention is conjugated to one or more maytansinoid molecules.

Maytansinoids are mitotic inhibitors which act by inhibiting tubulin polymerization. Maytansine was first isolated from the east African shrub *Maytenus serrata* (U.S. Patent No. 3,896,111). Subsequently, it was discovered that certain microbes also produce maytansinoids, such as maytansinol and C-3 maytansinol esters (U.S. Patent No. 4,151,042). Synthetic maytansinol and derivatives and analogues thereof are disclosed, for example, in U.S. Patent Nos. 4,137,230; 4,248,870; 4,256,746; 4,260,608; 4,265,814; 4,294,757; 4,307,016; 25 4,308,268; 4,308,269; 4,309,428; 4,313,946; 4,315,929; 4,317,821; 4,322,348; 4,331,598; 4,361,650; 4,364,866; 4,424,219; 4,450,254; 4,362,663; and 4,371,533, the disclosures of which are hereby expressly 30 incorporated by reference.

Maytansinoid-antibody conjugates

In an attempt to improve their therapeutic index, maytansine and maytansinoids have been conjugated to antibodies specifically binding to tumor cell antigens. Immunoconjugates containing maytansinoids and their therapeutic use are disclosed, for example, in U.S. Patent Nos. 5,208,020, 5,416,064 and European Patent EP

0 425 235 B1, the disclosures of which are hereby expressly incorporated by reference. Liu et al., Proc. Natl. Acad. Sci. USA 93:8618-8623 (1996) described immunoconjugates comprising a maytansinoid designated DM1 linked to the monoclonal antibody C242 directed against human colorectal cancer. The conjugate was found to be highly cytotoxic towards cultured colon cancer cells, and showed antitumor activity in an *in vivo* tumor growth assay. Chari et al., Cancer Research 52:127-131 (1992) describe immunoconjugates in which a maytansinoid was conjugated via a disulfide linker to the murine antibody A7 binding to an antigen on human colon cancer cell lines, or to another murine monoclonal antibody TA.1 that binds the HER-2/*neu* oncogene. The cytotoxicity of the TA.1-maytansinoid conjugate was tested *in vitro* on the human breast cancer cell line SK-BR-3, which expresses 3×10^5 HER-2 surface antigens per cell. The drug conjugate achieved a degree of cytotoxicity similar to the free maytansinoid drug, which could be increased by increasing the number of maytansinoid molecules per antibody molecule. The A7-maytansinoid conjugate showed low systemic cytotoxicity in mice.

Anti-TAT polypeptide antibody-maytansinoid conjugates (immunoconjugates)

Anti-TAT antibody-maytansinoid conjugates are prepared by chemically linking an anti-TAT antibody to a maytansinoid molecule without significantly diminishing the biological activity of either the antibody or the maytansinoid molecule. An average of 3-4 maytansinoid molecules conjugated per antibody molecule has shown efficacy in enhancing cytotoxicity of target cells without negatively affecting the function or solubility of the antibody, although even one molecule of toxin/antibody would be expected to enhance cytotoxicity over the use of naked antibody. Maytansinoids are well known in the art and can be synthesized by known techniques or isolated from natural sources. Suitable maytansinoids are disclosed, for example, in U.S. Patent No. 5,208,020 and in the other patents and nonpatent publications referred to hereinabove. Preferred maytansinoids are maytansinol and maytansinol analogues modified in the aromatic ring or at other positions of the maytansinol molecule, such as various maytansinol esters.

There are many linking groups known in the art for making antibody-maytansinoid conjugates, including, for example, those disclosed in U.S. Patent No. 5,208,020 or EP Patent 0 425 235 B1, and Chari et al., Cancer Research 52:127-131 (1992). The linking groups include disulfide groups, thioether groups, acid labile groups, photolabile groups, peptidase labile groups, or esterase labile groups, as disclosed in the above-identified patents, disulfide and thioether groups being preferred.

Conjugates of the antibody and maytansinoid may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridylthio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as toluene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). Particularly preferred coupling agents include N-succinimidyl-3-(2-pyridylthio) propionate (SPDP) (Carlsson et al. Biochem. J. 173:723-737 [1978]) and N-succinimidyl-4-(2-pyridylthio)pentanoate (SPP) to provide for a disulfide linkage.

The linker may be attached to the maytansinoid molecule at various positions, depending on the type of the link. For example, an ester linkage may be formed by reaction with a hydroxyl group using conventional coupling techniques. The reaction may occur at the C-3 position having a hydroxyl group, the C-14 position modified with hydroxymethyl, the C-15 position modified with a hydroxyl group, and the C-20 position having a hydroxyl group. In a preferred embodiment, the linkage is formed at the C-3 position of maytansinol or a maytansinol analogue.

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Calicheamicin

Another immunoconjugate of interest comprises an anti-TAT antibody conjugated to one or more calicheamicin molecules. The calicheamicin family of antibiotics are capable of producing double-stranded DNA breaks at sub-picomolar concentrations. For the preparation of conjugates of the calicheamicin family, see U.S. patents 5,712,374, 5,714,586, 5,739,116, 5,767,285, 5,770,701, 5,770,710, 5,773,001, 5,877,296 (all to American Cyanamid Company). Structural analogues of calicheamicin which may be used include, but are not limited to, γ_1^I , α_2^I , α_3^I , N-acetyl- γ_1^I , PSAG and θ^I_1 (Hinman et al., Cancer Research 53:3336-3342 (1993), Lode et al., Cancer Research 58:2925-2928 (1998) and the aforementioned U.S. patents to American Cyanamid). Another anti-tumor drug that the antibody can be conjugated is QFA which is an antifolate. Both calicheamicin and QFA have intracellular sites of action and do not readily cross the plasma membrane. Therefore, cellular uptake of these agents through antibody mediated internalization greatly enhances their cytotoxic effects.

Other cytotoxic agents

Other antitumor agents that can be conjugated to the anti-TAT antibodies of the invention include BCNU, streptozocin, vincristine and 5-fluorouracil, the family of agents known collectively LL-E33288 complex described in U.S. patents 5,053,394, 5,770,710, as well as esperamicins (U.S. patent 5,877,296).

Enzymatically active toxins and fragments thereof which can be used include diphtheria A chain, nonbinding active fragments of diphtheria toxin, exotoxin A chain (from *Pseudomonas aeruginosa*), ricin A chain, abrin A chain, modeccin A chain, alpha-sarcin, *Aleurites fordii* proteins, dianthin proteins, *Phytolaca americana* proteins (PAPI, PAPII, and PAP-S), momordica charantia inhibitor, curcin, crotin, sapaonaria officinalis inhibitor, gelonin, mitogellin, restrictocin, phenomycin, enomycin and the trichothecenes. See, for example, WO 93/21232 published October 28, 1993.

The present invention further contemplates an immunoconjugate formed between an antibody and a compound with nucleolytic activity (e.g., a ribonuclease or a DNA endonuclease such as a deoxyribonuclease; DNase).

For selective destruction of the tumor, the antibody may comprise a highly radioactive atom. A variety of radioactive isotopes are available for the production of radioconjugated anti-TAT antibodies. Examples include At²¹¹, I¹³¹, I¹²⁵, Y⁹⁰, Re¹⁸⁶, Re¹⁸⁸, Sm¹⁵³, Bi²¹², P³², Pb²¹² and radioactive isotopes of Lu. When the conjugate is used for diagnosis, it may comprise a radioactive atom for scintigraphic studies, for example tc^{99m} or I¹²³, or a spin label for nuclear magnetic resonance (NMR) imaging (also known as magnetic resonance

imaging, mri), such as iodine-123 again, iodine-131, indium-111, fluorine-19, carbon-13, nitrogen-15, oxygen-17, gadolinium, manganese or iron.

The radio- or other labels may be incorporated in the conjugate in known ways. For example, the peptide may be biosynthesized or may be synthesized by chemical amino acid synthesis using suitable amino acid precursors involving, for example, fluorine-19 in place of hydrogen. Labels such as tc^{99m} or I^{123} , Re^{186} , Re^{188} and In^{111} can be attached via a cysteine residue in the peptide. Yttrium-90 can be attached via a lysine residue. The IODOGEN method (Fraker et al (1978) *Biochem. Biophys. Res. Commun.* 80: 49-57 can be used to incorporate iodine-123. "Monoclonal Antibodies in Immunoscintigraphy" (Chatal, CRC Press 1989) describes other methods in detail.

Conjugates of the antibody and cytotoxic agent may be made using a variety of bifunctional protein coupling agents such as N-succinimidyl-3-(2-pyridylthio) propionate (SPDP), succinimidyl-4-(N-maleimidomethyl) cyclohexane-1-carboxylate, iminothiolane (IT), bifunctional derivatives of imidoesters (such as dimethyl adipimidate HCL), active esters (such as disuccinimidyl suberate), aldehydes (such as glutaraldehyde), bis-azido compounds (such as bis (p-azidobenzoyl) hexanediamine), bis-diazonium derivatives (such as bis-(p-diazoniumbenzoyl)-ethylenediamine), diisocyanates (such as tolyene 2,6-diisocyanate), and bis-active fluorine compounds (such as 1,5-difluoro-2,4-dinitrobenzene). For example, a ricin immunotoxin can be prepared as described in Vitetta et al., *Science* 238:1098 (1987). Carbon-14-labeled 1-isothiocyanatobenzyl-3-methyldiethylene triaminepentaacetic acid (MX-DTPA) is an exemplary chelating agent for conjugation of radionucleotide to the antibody. See WO94/11026. The linker may be a "cleavable linker" facilitating release of the cytotoxic drug in the cell. For example, an acid-labile linker, peptidase-sensitive linker, photolabile linker, dimethyl linker or disulfide-containing linker (Chari et al., *Cancer Research* 52:127-131 (1992); U.S. Patent No. 5,208,020) may be used.

Alternatively, a fusion protein comprising the anti-TAT antibody and cytotoxic agent may be made, e.g., by recombinant techniques or peptide synthesis. The length of DNA may comprise respective regions encoding the two portions of the conjugate either adjacent one another or separated by a region encoding a linker peptide which does not destroy the desired properties of the conjugate.

In yet another embodiment, the antibody may be conjugated to a "receptor" (such streptavidin) for utilization in tumor pre-targeting wherein the antibody-receptor conjugate is administered to the patient, followed by removal of unbound conjugate from the circulation using a clearing agent and then administration of a "ligand" (e.g., avidin) which is conjugated to a cytotoxic agent (e.g., a radionucleotide).

10. Immunoliposomes

The anti-TAT antibodies disclosed herein may also be formulated as immunoliposomes. A "liposome" is a small vesicle composed of various types of lipids, phospholipids and/or surfactant which is useful for delivery of a drug to a mammal. The components of the liposome are commonly arranged in a bilayer formation, similar to the lipid arrangement of biological membranes. Liposomes containing the antibody are prepared by methods known in the art, such as described in Epstein et al., *Proc. Natl. Acad. Sci. USA* 82:3688 (1985); Hwang et al., *Proc. Natl. Acad. Sci. USA* 77:4030 (1980); U.S. Pat. Nos. 4,485,045 and 4,544,545;

and WO97/38731 published October 23, 1997. Liposomes with enhanced circulation time are disclosed in U.S. Patent No. 5,013,556.

Particularly useful liposomes can be generated by the reverse phase evaporation method with a lipid composition comprising phosphatidylcholine, cholesterol and PEG-derivatized phosphatidylethanolamine (PEG-PE). Liposomes are extruded through filters of defined pore size to yield liposomes with the desired diameter. 5 Fab' fragments of the antibody of the present invention can be conjugated to the liposomes as described in Martin et al., *J. Biol. Chem.* 257:286-288 (1982) via a disulfide interchange reaction. A chemotherapeutic agent is optionally contained within the liposome. See Gabizon et al., *J. National Cancer Inst.* 81(19):1484 (1989).

10 **B. TAT Binding Oligopeptides**

TAT binding oligopeptides of the present invention are oligopeptides that bind, preferably specifically, to a TAT polypeptide as described herein. TAT binding oligopeptides may be chemically synthesized using known oligopeptide synthesis methodology or may be prepared and purified using recombinant technology. TAT binding oligopeptides are usually at least about 5 amino acids in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60, 61, 62, 63, 64, 65, 66, 67, 68, 69, 70, 71, 72, 73, 74, 75, 76, 77, 78, 79, 80, 81, 82, 83, 84, 85, 86, 87, 88, 89, 90, 91, 92, 93, 94, 95, 96, 97, 98, 99, or 100 amino acids in length or more, wherein such oligopeptides that are capable of binding, preferably specifically, to a TAT polypeptide as described herein. TAT binding oligopeptides may be identified without undue experimentation using well known techniques. In this regard, it is noted that 15 techniques for screening oligopeptide libraries for oligopeptides that are capable of specifically binding to a polypeptide target are well known in the art (see, e.g., U.S. Patent Nos. 5,556,762, 5,750,373, 4,708,871, 4,833,092, 5,223,409, 5,403,484, 5,571,689, 5,663,143; PCT Publication Nos. WO 84/03506 and WO84/03564; Geysen et al., *Proc. Natl. Acad. Sci. U.S.A.*, 81:3998-4002 (1984); Geysen et al., *Proc. Natl. Acad. Sci. U.S.A.*, 82:178-182 (1985); Geysen et al., in *Synthetic Peptides as Antigens*, 130-149 (1986); 20 Geysen et al., *J. Immunol. Meth.*, 102:259-274 (1987); Schoofs et al., *J. Immunol.*, 140:611-616 (1988), Geysen et al., *Proc. Natl. Acad. Sci. USA*, 87:6378; Lowman, H.B. et al. (1991) *Biochemistry*, 30:10832; Clackson, T. et al. (1991) *Nature*, 352: 624; Marks, J. D. et al. (1991), *J. Mol. Biol.*, 222:581; Kang, A.S. et al. (1991) *Proc. Natl. Acad. Sci. USA*, 88:8363, and Smith, G. P. (1991) *Current Opin. Biotechnol.*, 2:668).

30 In this regard, bacteriophage (phage) display is one well known technique which allows one to screen large oligopeptide libraries to identify member(s) of those libraries which are capable of specifically binding to a polypeptide target. Phage display is a technique by which variant polypeptides are displayed as fusion proteins to the coat protein on the surface of bacteriophage particles (Scott, J.K. and Smith, G. P. (1990) *Science* 249: 386). The utility of phage display lies in the fact that large libraries of selectively randomized protein variants (or randomly cloned cDNAs) can be rapidly and efficiently sorted for those sequences that bind 35 to a target molecule with high affinity. Display of peptide (Cwirla, S. E. et al. (1990) *Proc. Natl. Acad. Sci.*

USA, 87:6378) or protein (Lowman, H.B. et al. (1991) *Biochemistry*, 30:10832; Clackson, T. et al. (1991) *Nature*, 352: 624; Marks, J. D. et al. (1991), *J. Mol. Biol.*, 222:581; Kang, A.S. et al. (1991) *Proc. Natl. Acad. Sci. USA*, 88:8363) libraries on phage have been used for screening millions of polypeptides or oligopeptides for ones with specific binding properties (Smith, G. P. (1991) *Current Opin. Biotechnol.*, 2:668). Sorting phage libraries of random mutants requires a strategy for constructing and propagating a large number of variants, a procedure for affinity purification using the target receptor, and a means of evaluating the results of binding enrichments. U.S. Patent Nos. 5,223,409, 5,403,484, 5,571,689, and 5,663,143.

5 Although most phage display methods have used filamentous phage, lambdoid phage display systems (WO 95/34683; U.S. 5,627,024), T4 phage display systems (Ren, Z-J. et al. (1998) *Gene* 215:439; Zhu, Z. (1997) *CAN* 33:534; Jiang, J. et al. (1997) *CAN* 128:44380; Ren, Z-J. et al. (1997) *CAN* 127:215644; Ren, Z-J. (1996) *Protein Sci.* 5:1833; Efimov, V. P. et al. (1995) *Virus Genes* 10:173) and T7 phage display systems (Smith, G. P. and Scott, J.K. (1993) *Methods in Enzymology*, 217, 228–257; U.S. 5,766,905) are also known.

10 Many other improvements and variations of the basic phage display concept have now been developed. These improvements enhance the ability of display systems to screen peptide libraries for binding to selected target molecules and to display functional proteins with the potential of screening these proteins for desired properties. Combinatorial reaction devices for phage display reactions have been developed (WO 98/14277) and phage display libraries have been used to analyze and control bimolecular interactions (WO 98/20169; WO 98/20159) and properties of constrained helical peptides (WO 98/20036). WO 97/35196 describes a method of isolating an affinity ligand in which a phage display library is contacted with one solution in which the ligand will bind to a target molecule and a second solution in which the affinity ligand will not bind to the target 15 molecule, to selectively isolate binding ligands. WO 97/46251 describes a method of biopanning a random phage display library with an affinity purified antibody and then isolating binding phage, followed by a micropanning process using microplate wells to isolate high affinity binding phage. The use of *Staphylococcus aureus* protein A as an affinity tag has also been reported (Li et al. (1998) *Mol Biotech.*, 9:187). WO 97/47314 describes the use of substrate subtraction libraries to distinguish enzyme specificities using a combinatorial 20 library which may be a phage display library. A method for selecting enzymes suitable for use in detergents using phage display is described in WO 97/09446. Additional methods of selecting specific binding proteins 25 are described in U.S. Patent Nos. 5,498,538, 5,432,018, and WO 98/15833.

Methods of generating peptide libraries and screening these libraries are also disclosed in U.S. Patent Nos. 5,723,286, 5,432,018, 5,580,717, 5,427,908, 5,498,530, 5,770,434, 5,734,018, 5,698,426, 5,763,192, 30 and 5,723,323.

C. TAT Binding Organic Molecules

TAT binding organic molecules are organic molecules other than oligopeptides or antibodies as defined herein that bind, preferably specifically, to a TAT polypeptide as described herein. TAT binding organic molecules may be identified and chemically synthesized using known methodology (see, e.g., PCT Publication 35 Nos. WO00/00823 and WO00/39585). TAT binding organic molecules are usually less than about 2000 daltons in size, alternatively less than about 1500, 750, 500, 250 or 200 daltons in size, wherein such organic molecules

that are capable of binding, preferably specifically, to a TAT polypeptide as described herein may be identified without undue experimentation using well known techniques. In this regard, it is noted that techniques for screening organic molecule libraries for molecules that are capable of binding to a polypeptide target are well known in the art (see, e.g., PCT Publication Nos. WO00/00823 and WO00/39585). TAT binding organic molecules may be, for example, aldehydes, ketones, oximes, hydrazones, semicarbazones, carbazides, primary amines, secondary amines, tertiary amines, N-substituted hydrazines, hydrazides, alcohols, ethers, thiols, 5 thioethers, disulfides, carboxylic acids, esters, amides, ureas, carbamates, carbonates, ketals, thioketals, acetals, thioacetals, aryl halides, aryl sulfonates, alkyl halides, alkyl sulfonates, aromatic compounds, heterocyclic compounds, anilines, alkenes, alkynes, diols, amino alcohols, oxazolidines, oxazolines, thiazolidines, thiazolines, enamines, sulfonamides, epoxides, aziridines, isocyanates, sulfonyl chlorides, diazo compounds, 10 acid chlorides, or the like.

10 D. Screening for Anti-TAT Antibodies, TAT Binding Oligopeptides and TAT Binding Organic Molecules With the Desired Properties

15 Techniques for generating antibodies, oligopeptides and organic molecules that bind to TAT polypeptides have been described above. One may further select antibodies, oligopeptides or other organic molecules with certain biological characteristics, as desired.

20 The growth inhibitory effects of an anti-TAT antibody, oligopeptide or other organic molecule of the invention may be assessed by methods known in the art, e.g., using cells which express a TAT polypeptide either endogenously or following transfection with the TAT gene. For example, appropriate tumor cell lines and TAT-transfected cells may be treated with an anti-TAT monoclonal antibody, oligopeptide or other organic molecule of the invention at various concentrations for a few days (e.g., 2-7) days and stained with crystal violet or MTT or analyzed by some other colorimetric assay. Another method of measuring proliferation would be by comparing ³H-thymidine uptake by the cells treated in the presence or absence of an anti-TAT antibody, TAT binding oligopeptide or TAT binding organic molecule of the invention. After treatment, the cells are harvested and the amount of radioactivity incorporated into the DNA quantitated in a scintillation counter. Appropriate 25 positive controls include treatment of a selected cell line with a growth inhibitory antibody known to inhibit growth of that cell line. Growth inhibition of tumor cells *in vivo* can be determined in various ways known in the art. Preferably, the tumor cell is one that overexpresses a TAT polypeptide. Preferably, the anti-TAT antibody, TAT binding oligopeptide or TAT binding organic molecule will inhibit cell proliferation of a TAT-expressing tumor cell *in vitro* or *in vivo* by about 25-100% compared to the untreated tumor cell, more 30 preferably, by about 30-100%, and even more preferably by about 50-100% or 70-100%, in one embodiment, at an antibody concentration of about 0.5 to 30 μ g/ml. Growth inhibition can be measured at an antibody concentration of about 0.5 to 30 μ g/ml or about 0.5 nM to 200 nM in cell culture, where the growth inhibition is determined 1-10 days after exposure of the tumor cells to the antibody. The antibody is growth inhibitory *in vivo* if administration of the anti-TAT antibody at about 1 μ g/kg to about 100 mg/kg body weight results in 35 reduction in tumor size or reduction of tumor cell proliferation within about 5 days to 3 months from the first administration of the antibody, preferably within about 5 to 30 days.

To select for an anti-TAT antibody, TAT binding oligopeptide or TAT binding organic molecule which induces cell death, loss of membrane integrity as indicated by, e.g., propidium iodide (PI), trypan blue or 7AAD uptake may be assessed relative to control. A PI uptake assay can be performed in the absence of complement and immune effector cells. TAT polypeptide-expressing tumor cells are incubated with medium alone or medium containing the appropriate anti-TAT antibody (e.g., at about 10 µg/ml), TAT binding oligopeptide or TAT binding organic molecule. The cells are incubated for a 3 day time period. Following each treatment, 5 cells are washed and aliquoted into 35 mm strainer-capped 12 x 75 tubes (1ml per tube, 3 tubes per treatment group) for removal of cell clumps. Tubes then receive PI (10 µg/ml). Samples may be analyzed using a FACSCAN® flow cytometer and FACSCONVERT® CellQuest software (Becton Dickinson). Those anti-TAT 10 antibodies, TAT binding oligopeptides or TAT binding organic molecules that induce statistically significant levels of cell death as determined by PI uptake may be selected as cell death-inducing anti-TAT antibodies, TAT binding oligopeptides or TAT binding organic molecules.

To screen for antibodies, oligopeptides or other organic molecules which bind to an epitope on a TAT polypeptide bound by an antibody of interest, a routine cross-blocking assay such as that described in Antibodies, A Laboratory Manual, Cold Spring Harbor Laboratory, Ed Harlow and David Lane (1988), can 15 be performed. This assay can be used to determine if a test antibody, oligopeptide or other organic molecule binds the same site or epitope as a known anti-TAT antibody. Alternatively, or additionally, epitope mapping can be performed by methods known in the art. For example, the antibody sequence can be mutagenized such as by alanine scanning, to identify contact residues. The mutant antibody is initially tested for binding with polyclonal antibody to ensure proper folding. In a different method, peptides corresponding to different regions 20 of a TAT polypeptide can be used in competition assays with the test antibodies or with a test antibody and an antibody with a characterized or known epitope.

E. Antibody Dependent Enzyme Mediated Prodrug Therapy (ADEPT)

The antibodies of the present invention may also be used in ADEPT by conjugating the antibody to a prodrug-activating enzyme which converts a prodrug (e.g., a peptidyl chemotherapeutic agent, see 25 WO81/01145) to an active anti-cancer drug. See, for example, WO 88/07378 and U.S. Patent No. 4,975,278.

The enzyme component of the immunoconjugate useful for ADEPT includes any enzyme capable of acting on a prodrug in such a way so as to convert it into its more active, cytotoxic form.

Enzymes that are useful in the method of this invention include, but are not limited to, alkaline phosphatase useful for converting phosphate-containing prodrugs into free drugs; arylsulfatase useful for 30 converting sulfate-containing prodrugs into free drugs; cytosine deaminase useful for converting non-toxic 5-fluorocytosine into the anti-cancer drug, 5-fluorouracil; proteases, such as serratia protease, thermolysin, subtilisin, carboxypeptidases and cathepsins (such as cathepsins B and L), that are useful for converting peptide-containing prodrugs into free drugs; D-alanylcarboxypeptidases, useful for converting prodrugs that contain D-amino acid substituents; carbohydrate-cleaving enzymes such as β -galactosidase and neuraminidase useful for 35 converting glycosylated prodrugs into free drugs; β -lactamase useful for converting drugs derivatized with β -lactams into free drugs; and penicillin amidases, such as penicillin V amidase or penicillin G amidase, useful

for converting drugs derivatized at their amine nitrogens with phenoxyacetyl or phenylacetyl groups, respectively, into free drugs. Alternatively, antibodies with enzymatic activity, also known in the art as "abzymes", can be used to convert the prodrugs of the invention into free active drugs (see, e.g., Massey, *Nature* 328:457-458 (1987)). Antibody-abzyme conjugates can be prepared as described herein for delivery of the abzyme to a tumor cell population.

5 The enzymes of this invention can be covalently bound to the anti-TAT antibodies by techniques well known in the art such as the use of the heterobifunctional crosslinking reagents discussed above. Alternatively, fusion proteins comprising at least the antigen binding region of an antibody of the invention linked to at least a functionally active portion of an enzyme of the invention can be constructed using recombinant DNA techniques well known in the art (see, e.g., Neuberger et al., *Nature* 312:604-608 (1984)).

10 F. Full-Length TAT Polypeptides

The present invention also provides newly identified and isolated nucleotide sequences encoding polypeptides referred to in the present application as TAT polypeptides. In particular, cDNAs (partial and full-length) encoding various TAT polypeptides have been identified and isolated, as disclosed in further detail in the Examples below.

15 As disclosed in the Examples below, various cDNA clones have been deposited with the ATCC. The actual nucleotide sequences of those clones can readily be determined by the skilled artisan by sequencing of the deposited clone using routine methods in the art. The predicted amino acid sequence can be determined from the nucleotide sequence using routine skill. For the TAT polypeptides and encoding nucleic acids described herein, in some cases, Applicants have identified what is believed to be the reading frame best identifiable with the sequence information available at the time.

20 G. Anti-TAT Antibody and TAT Polypeptide Variants

In addition to the anti-TAT antibodies and full-length native sequence TAT polypeptides described herein, it is contemplated that anti-TAT antibody and TAT polypeptide variants can be prepared. Anti-TAT antibody and TAT polypeptide variants can be prepared by introducing appropriate nucleotide changes into the 25 encoding DNA, and/or by synthesis of the desired antibody or polypeptide. Those skilled in the art will appreciate that amino acid changes may alter post-translational processes of the anti-TAT antibody or TAT polypeptide, such as changing the number or position of glycosylation sites or altering the membrane anchoring characteristics.

30 Variations in the anti-TAT antibodies and TAT polypeptides described herein, can be made, for example, using any of the techniques and guidelines for conservative and non-conservative mutations set forth, for instance, in U.S. Patent No. 5,364,934. Variations may be a substitution, deletion or insertion of one or more codons encoding the antibody or polypeptide that results in a change in the amino acid sequence as compared with the native sequence antibody or polypeptide. Optionally the variation is by substitution of at least one amino acid with any other amino acid in one or more of the domains of the anti-TAT antibody or TAT 35 polypeptide. Guidance in determining which amino acid residue may be inserted, substituted or deleted without adversely affecting the desired activity may be found by comparing the sequence of the anti-TAT antibody or

TAT polypeptide with that of homologous known protein molecules and minimizing the number of amino acid sequence changes made in regions of high homology. Amino acid substitutions can be the result of replacing one amino acid with another amino acid having similar structural and/or chemical properties, such as the replacement of a leucine with a serine, i.e., conservative amino acid replacements. Insertions or deletions may optionally be in the range of about 1 to 5 amino acids. The variation allowed may be determined by 5 systematically making insertions, deletions or substitutions of amino acids in the sequence and testing the resulting variants for activity exhibited by the full-length or mature native sequence.

Anti-TAT antibody and TAT polypeptide fragments are provided herein. Such fragments may be truncated at the N-terminus or C-terminus, or may lack internal residues, for example, when compared with a full length native antibody or protein. Certain fragments lack amino acid residues that are not essential for 10 a desired biological activity of the anti-TAT antibody or TAT polypeptide.

Anti-TAT antibody and TAT polypeptide fragments may be prepared by any of a number of conventional techniques. Desired peptide fragments may be chemically synthesized. An alternative approach involves generating antibody or polypeptide fragments by enzymatic digestion, e.g., by treating the protein with an enzyme known to cleave proteins at sites defined by particular amino acid residues, or by digesting the DNA 15 with suitable restriction enzymes and isolating the desired fragment. Yet another suitable technique involves isolating and amplifying a DNA fragment encoding a desired antibody or polypeptide fragment, by polymerase chain reaction (PCR). Oligonucleotides that define the desired termini of the DNA fragment are employed at the 5' and 3' primers in the PCR. Preferably, anti-TAT antibody and TAT polypeptide fragments share at least one biological and/or immunological activity with the native anti-TAT antibody or TAT polypeptide disclosed 20 herein.

In particular embodiments, conservative substitutions of interest are shown in Table 6 under the heading of preferred substitutions. If such substitutions result in a change in biological activity, then more substantial changes, denominated exemplary substitutions in Table 6, or as further described below in reference to amino acid classes, are introduced and the products screened.

Table 6

| | <u>Original Residue</u> | <u>Exemplary Substitutions</u> | <u>Preferred Substitutions</u> |
|----|-------------------------|-------------------------------------|--------------------------------|
| 5 | Ala (A) | val; leu; ile | val |
| | Arg (R) | lys; gln; asn | lys |
| | Asn (N) | gln; his; lys; arg | gln |
| | Asp (D) | glu | glu |
| | Cys (C) | ser | ser |
| | Gln (Q) | asn | asn |
| 10 | Glu (E) | asp | asp |
| | Gly (G) | pro; ala | ala |
| | His (H) | asn; gln; lys; arg | arg |
| | Ile (I) | leu; val; met; ala; phe; norleucine | leu |
| 15 | Leu (L) | norleucine; ile; val; met; ala; phe | ile |
| | Lys (K) | arg; gln; asn | arg |
| | Met (M) | leu; phe; ile | leu |
| | Phe (F) | leu; val; ile; ala; tyr | leu |
| | Pro (P) | ala | ala |
| | Ser (S) | thr | thr |
| 20 | Thr (T) | ser | ser |
| | Trp (W) | tyr; phe | tyr |
| | Tyr (Y) | trp; phe; thr; ser | phe |
| | Val (V) | ile; leu; met; phe; ala; norleucine | leu |

Substantial modifications in function or immunological identity of the anti-TAT antibody or TAT polypeptide are accomplished by selecting substitutions that differ significantly in their effect on maintaining 30 (a) the structure of the polypeptide backbone in the area of the substitution, for example, as a sheet or helical conformation, (b) the charge or hydrophobicity of the molecule at the target site, or (c) the bulk of the side chain. Naturally occurring residues are divided into groups based on common side-chain properties:

- (1) hydrophobic: norleucine, met, ala, val, leu, ile;
- (2) neutral hydrophilic: cys, ser, thr;
- (3) acidic: asp, glu;
- (4) basic: asn, gln, his, lys, arg;
- (5) residues that influence chain orientation: gly, pro; and
- (6) aromatic: trp, tyr, phe.

Non-conservative substitutions will entail exchanging a member of one of these classes for another 40 class. Such substituted residues also may be introduced into the conservative substitution sites or, more preferably, into the remaining (non-conserved) sites.

The variations can be made using methods known in the art such as oligonucleotide-mediated (site-directed) mutagenesis, alanine scanning, and PCR mutagenesis. Site-directed mutagenesis [Carter et al. *Nucl. Acids Res.*, 13:4331 (1986); Zoller et al., *Nucl. Acids Res.*, 10:6487 (1987)], cassette mutagenesis [Wells et al., *Gene*, 34:315 (1985)], restriction selection mutagenesis [Wells et al., *Philos. Trans. R. Soc. London SerA*, 317:415 (1986)] or other known techniques can be performed on the cloned DNA to produce the anti-TAT antibody or TAT polypeptide variant DNA.

Scanning amino acid analysis can also be employed to identify one or more amino acids along a contiguous sequence. Among the preferred scanning amino acids are relatively small, neutral amino acids. Such amino acids include alanine, glycine, serine, and cysteine. Alanine is typically a preferred scanning amino acid among this group because it eliminates the side-chain beyond the beta-carbon and is less likely to alter the main-chain conformation of the variant [Cunningham and Wells, *Science*, 244:1081-1085 (1989)]. Alanine is also typically preferred because it is the most common amino acid. Further, it is frequently found in both buried and exposed positions [Creighton, *The Proteins*, (W.H. Freeman & Co., N.Y.); Chothia, *J. Mol. Biol.*, 150:1 (1976)]. If alanine substitution does not yield adequate amounts of variant, an isoteric amino acid can be used.

Any cysteine residue not involved in maintaining the proper conformation of the anti-TAT antibody or TAT polypeptide also may be substituted, generally with serine, to improve the oxidative stability of the molecule and prevent aberrant crosslinking. Conversely, cysteine bond(s) may be added to the anti-TAT antibody or TAT polypeptide to improve its stability (particularly where the antibody is an antibody fragment such as an Fv fragment).

A particularly preferred type of substitutional variant involves substituting one or more hypervariable region residues of a parent antibody (e.g., a humanized or human antibody). Generally, the resulting variant(s) selected for further development will have improved biological properties relative to the parent antibody from which they are generated. A convenient way for generating such substitutional variants involves affinity maturation using phage display. Briefly, several hypervariable region sites (e.g., 6-7 sites) are mutated to generate all possible amino substitutions at each site. The antibody variants thus generated are displayed in a monovalent fashion from filamentous phage particles as fusions to the gene III product of M13 packaged within each particle. The phage-displayed variants are then screened for their biological activity (e.g., binding affinity) as herein disclosed. In order to identify candidate hypervariable region sites for modification, alanine scanning mutagenesis can be performed to identify hypervariable region residues contributing significantly to antigen binding. Alternatively, or additionally, it may be beneficial to analyze a crystal structure of the antigen-antibody complex to identify contact points between the antibody and human TAT polypeptide. Such contact residues and neighboring residues are candidates for substitution according to the techniques elaborated herein. Once such variants are generated, the panel of variants is subjected to screening as described herein and antibodies with superior properties in one or more relevant assays may be selected for further development.

Nucleic acid molecules encoding amino acid sequence variants of the anti-TAT antibody are prepared by a variety of methods known in the art. These methods include, but are not limited to, isolation from a natural source (in the case of naturally occurring amino acid sequence variants) or preparation by oligonucleotide-

mediated (or site-directed) mutagenesis, PCR mutagenesis, and cassette mutagenesis of an earlier prepared variant or a non-variant version of the anti-TAT antibody.

H. Modifications of Anti-TAT Antibodies and TAT Polypeptides

Covalent modifications of anti-TAT antibodies and TAT polypeptides are included within the scope of this invention. One type of covalent modification includes reacting targeted amino acid residues of an anti-TAT antibody or TAT polypeptide with an organic derivatizing agent that is capable of reacting with selected side chains or the N- or C-terminal residues of the anti-TAT antibody or TAT polypeptide. Derivatization with bifunctional agents is useful, for instance, for crosslinking anti-TAT antibody or TAT polypeptide to a water-insoluble support matrix or surface for use in the method for purifying anti-TAT antibodies, and vice-versa. Commonly used crosslinking agents include, e.g., 1,1-bis(diazoacetyl)-2-phenylethane, glutaraldehyde, N-hydroxysuccinimide esters, for example, esters with 4-azidosalicylic acid, homobifunctional imidoesters, including disuccinimidyl esters such as 3,3'-dithiobis(succinimidylpropionate), bifunctional maleimides such as bis-N-maleimido-1,8-octane and agents such as methyl-3-[(p-azidophenyl)dithio]propioimidate.

Other modifications include deamidation of glutaminyl and asparaginyl residues to the corresponding glutamyl and aspartyl residues, respectively, hydroxylation of proline and lysine, phosphorylation of hydroxyl groups of seryl or threonyl residues, methylation of the α -amino groups of lysine, arginine, and histidine side chains [T.E. Creighton, Proteins: Structure and Molecular Properties, W.H. Freeman & Co., San Francisco, pp. 79-86 (1983)], acetylation of the N-terminal amine, and amidation of any C-terminal carboxyl group.

Another type of covalent modification of the anti-TAT antibody or TAT polypeptide included within the scope of this invention comprises altering the native glycosylation pattern of the antibody or polypeptide. "Altering the native glycosylation pattern" is intended for purposes herein to mean deleting one or more carbohydrate moieties found in native sequence anti-TAT antibody or TAT polypeptide (either by removing the underlying glycosylation site or by deleting the glycosylation by chemical and/or enzymatic means), and/or adding one or more glycosylation sites that are not present in the native sequence anti-TAT antibody or TAT polypeptide. In addition, the phrase includes qualitative changes in the glycosylation of the native proteins, involving a change in the nature and proportions of the various carbohydrate moieties present.

Glycosylation of antibodies and other polypeptides is typically either N-linked or O-linked. N-linked refers to the attachment of the carbohydrate moiety to the side chain of an asparagine residue. The tripeptide sequences asparagine-X-serine and asparagine-X-threonine, where X is any amino acid except proline, are the recognition sequences for enzymatic attachment of the carbohydrate moiety to the asparagine side chain. Thus, the presence of either of these tripeptide sequences in a polypeptide creates a potential glycosylation site. O-linked glycosylation refers to the attachment of one of the sugars N-acetylglucosamine, galactose, or xylose to a hydroxyamino acid, most commonly serine or threonine, although 5-hydroxyproline or 5-hydroxylysine may also be used.

Addition of glycosylation sites to the anti-TAT antibody or TAT polypeptide is conveniently accomplished by altering the amino acid sequence such that it contains one or more of the above-described tripeptide sequences (for N-linked glycosylation sites). The alteration may also be made by the addition of, or substitution by, one or more serine or threonine residues to the sequence of the original anti-TAT antibody or TAT polypeptide (for O-linked glycosylation sites). The anti-TAT antibody or TAT polypeptide amino acid sequence may optionally be altered through changes at the DNA level, particularly by mutating the DNA encoding the anti-TAT antibody or TAT polypeptide at preselected bases such that codons are generated that will translate into the desired amino acids.

Another means of increasing the number of carbohydrate moieties on the anti-TAT antibody or TAT polypeptide is by chemical or enzymatic coupling of glycosides to the polypeptide. Such methods are described in the art, e.g., in WO 87/05330 published 11 September 1987, and in Aplin and Wriston, CRC Crit. Rev. Biochem., pp. 259-306 (1981).

Removal of carbohydrate moieties present on the anti-TAT antibody or TAT polypeptide may be accomplished chemically or enzymatically or by mutational substitution of codons encoding for amino acid residues that serve as targets for glycosylation. Chemical deglycosylation techniques are known in the art and described, for instance, by Hakimuddin, et al., Arch. Biochem. Biophys., 259:52 (1987) and by Edge et al., Anal. Biochem., 118:131 (1981). Enzymatic cleavage of carbohydrate moieties on polypeptides can be achieved by the use of a variety of endo- and exo-glycosidases as described by Thotakura et al., Meth. Enzymol., 138:350 (1987).

Another type of covalent modification of anti-TAT antibody or TAT polypeptide comprises linking the antibody or polypeptide to one of a variety of nonproteinaceous polymers, e.g., polyethylene glycol (PEG), polypropylene glycol, or polyoxyalkylenes, in the manner set forth in U.S. Patent Nos. 4,640,835; 4,496,689; 4,301,144; 4,670,417; 4,791,192 or 4,179,337. The antibody or polypeptide also may be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization (for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively), in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nanoparticles and nanocapsules), or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, 16th edition, Oslo, A., Ed., (1980).

The anti-TAT antibody or TAT polypeptide of the present invention may also be modified in a way to form chimeric molecules comprising an anti-TAT antibody or TAT polypeptide fused to another, heterologous polypeptide or amino acid sequence.

In one embodiment, such a chimeric molecule comprises a fusion of the anti-TAT antibody or TAT polypeptide with a tag polypeptide which provides an epitope to which an anti-tag antibody can selectively bind. The epitope tag is generally placed at the amino- or carboxyl- terminus of the anti-TAT antibody or TAT polypeptide. The presence of such epitope-tagged forms of the anti-TAT antibody or TAT polypeptide can be detected using an antibody against the tag polypeptide. Also, provision of the epitope tag enables the anti-TAT

antibody or TAT polypeptide to be readily purified by affinity purification using an anti-tag antibody or another type of affinity matrix that binds to the epitope tag. Various tag polypeptides and their respective antibodies are well known in the art. Examples include poly-histidine (poly-his) or poly-histidine-glycine (poly-his-gly) tags; the flu HA tag polypeptide and its antibody 12CA5 [Field et al., Mol. Cell. Biol., **8**:2159-2165 (1988)]; the c-myc tag and the 8F9, 3C7, 6E10, G4, B7 and 9E10 antibodies thereto [Evan et al., Molecular and Cellular Biology, **5**:3610-3616 (1985)]; and the Herpes Simplex virus glycoprotein D (gD) tag and its antibody [Paborsky et al., Protein Engineering, **3**(6):547-553 (1990)]. Other tag polypeptides include the Flag-peptide [Hopp et al., BioTechnology, **6**:1204-1210 (1988)]; the KT3 epitope peptide [Martin et al., Science, **255**:192-194 (1992)]; an α -tubulin epitope peptide [Skinner et al., J. Biol. Chem., **266**:15163-15166 (1991)]; and the T7 gene 10 protein peptide tag [Lutz-Freyermuth et al., Proc. Natl. Acad. Sci. USA, **87**:6393-6397 (1990)].

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In an alternative embodiment, the chimeric molecule may comprise a fusion of the anti-TAT antibody or TAT polypeptide with an immunoglobulin or a particular region of an immunoglobulin. For a bivalent form of the chimeric molecule (also referred to as an "immunoadhesin"), such a fusion could be to the Fc region of an IgG molecule. The Ig fusions preferably include the substitution of a soluble (transmembrane domain deleted or inactivated) form of an anti-TAT antibody or TAT polypeptide in place of at least one variable region within an Ig molecule. In a particularly preferred embodiment, the immunoglobulin fusion includes the hinge, CH_2 and CH_3 , or the hinge, CH_1 , CH_2 and CH_3 regions of an IgG1 molecule. For the production of immunoglobulin fusions see also US Patent No. 5,428,130 issued June 27, 1995.

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I. Preparation of Anti-TAT Antibodies and TAT Polypeptides

The description below relates primarily to production of anti-TAT antibodies and TAT polypeptides by culturing cells transformed or transfected with a vector containing anti-TAT antibody- and TAT polypeptide-encoding nucleic acid. It is, of course, contemplated that alternative methods, which are well known in the art, may be employed to prepare anti-TAT antibodies and TAT polypeptides. For instance, the appropriate amino acid sequence, or portions thereof, may be produced by direct peptide synthesis using solid-phase techniques [see, e.g., Stewart et al., Solid-Phase Peptide Synthesis, W.H. Freeman Co., San Francisco, CA (1969); Merrifield, J. Am. Chem. Soc., **85**:2149-2154 (1963)]. *In vitro* protein synthesis may be performed using manual techniques or by automation. Automated synthesis may be accomplished, for instance, using an Applied Biosystems Peptide Synthesizer (Foster City, CA) using manufacturer's instructions. Various portions of the anti-TAT antibody or TAT polypeptide may be chemically synthesized separately and combined using chemical or enzymatic methods to produce the desired anti-TAT antibody or TAT polypeptide.

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1. Isolation of DNA Encoding Anti-TAT Antibody or TAT Polypeptide

DNA encoding anti-TAT antibody or TAT polypeptide may be obtained from a cDNA library prepared from tissue believed to possess the anti-TAT antibody or TAT polypeptide mRNA and to express it at a detectable level. Accordingly, human anti-TAT antibody or TAT polypeptide DNA can be conveniently obtained from a cDNA library prepared from human tissue. The anti-TAT antibody- or TAT polypeptide-encoding gene may also be obtained from a genomic library or by known synthetic procedures (e.g., automated

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nucleic acid synthesis).

Libraries can be screened with probes (such as oligonucleotides of at least about 20-80 bases) designed to identify the gene of interest or the protein encoded by it. Screening the cDNA or genomic library with the selected probe may be conducted using standard procedures, such as described in Sambrook et al., Molecular Cloning: A Laboratory Manual (New York: Cold Spring Harbor Laboratory Press, 1989). An alternative means to isolate the gene encoding anti-TAT antibody or TAT polypeptide is to use PCR methodology [Sambrook et al., supra; Dieffenbach et al., PCR Primer: A Laboratory Manual (Cold Spring Harbor Laboratory Press, 1995)].

Techniques for screening a cDNA library are well known in the art. The oligonucleotide sequences selected as probes should be of sufficient length and sufficiently unambiguous that false positives are minimized. The oligonucleotide is preferably labeled such that it can be detected upon hybridization to DNA in the library being screened. Methods of labeling are well known in the art, and include the use of radiolabels like ^{32}P -labeled ATP, biotinylation or enzyme labeling. Hybridization conditions, including moderate stringency and high stringency, are provided in Sambrook et al., supra.

Sequences identified in such library screening methods can be compared and aligned to other known sequences deposited and available in public databases such as GenBank or other private sequence databases. Sequence identity (at either the amino acid or nucleotide level) within defined regions of the molecule or across the full-length sequence can be determined using methods known in the art and as described herein.

Nucleic acid having protein coding sequence may be obtained by screening selected cDNA or genomic libraries using the deduced amino acid sequence disclosed herein for the first time, and, if necessary, using conventional primer extension procedures as described in Sambrook et al., supra, to detect precursors and processing intermediates of mRNA that may not have been reverse-transcribed into cDNA.

2. Selection and Transformation of Host Cells

Host cells are transfected or transformed with expression or cloning vectors described herein for anti-TAT antibody or TAT polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences. The culture conditions, such as media, temperature, pH and the like, can be selected by the skilled artisan without undue experimentation. In general, principles, protocols, and practical techniques for maximizing the productivity of cell cultures can be found in Mammalian Cell Biotechnology: a Practical Approach, M. Butler, ed. (IRL Press, 1991) and Sambrook et al., supra.

Methods of eukaryotic cell transfection and prokaryotic cell transformation are known to the ordinarily skilled artisan, for example, CaCl_2 , CaPO_4 , liposome-mediated and electroporation. Depending on the host cell used, transformation is performed using standard techniques appropriate to such cells. The calcium treatment employing calcium chloride, as described in Sambrook et al., supra, or electroporation is generally used for prokaryotes. Infection with *Agrobacterium tumefaciens* is used for transformation of certain plant cells, as described by Shaw et al., Gene, 23:315 (1983) and WO 89/05859 published 29 June 1989. For mammalian cells without such cell walls, the calcium phosphate precipitation method of Graham and van der Eb, Virology,

52:456-457 (1978) can be employed. General aspects of mammalian cell host system transfections have been described in U.S. Patent No. 4,399,216. Transformations into yeast are typically carried out according to the method of Van Solingen et al., *J. Bact.*, 130:946 (1977) and Hsiao et al., *Proc. Natl. Acad. Sci. (USA)*, 76:3829 (1979). However, other methods for introducing DNA into cells, such as by nuclear microinjection, electroporation, bacterial protoplast fusion with intact cells, or polycations, e.g., polybrene, polyornithine, may also be used. For various techniques for transforming mammalian cells, see Keown et al., *Methods in Enzymology*, 185:527-537 (1990) and Mansour et al., *Nature*, 336:348-352 (1988).

10 Suitable host cells for cloning or expressing the DNA in the vectors herein include prokaryote, yeast, or higher eukaryote cells. Suitable prokaryotes include but are not limited to eubacteria, such as Gram-negative or Gram-positive organisms, for example, Enterobacteriaceae such as *E. coli*. Various *E. coli* strains are publicly available, such as *E. coli* K12 strain MM294 (ATCC 31,446); *E. coli* X1776 (ATCC 31,537); *E. coli* strain W3110 (ATCC 27,325) and K5 772 (ATCC 53,635). Other suitable prokaryotic host cells include Enterobacteriaceae such as *Escherichia*, e.g., *E. coli*, *Enterobacter*, *Erwinia*, *Klebsiella*, *Proteus*, *Salmonella*, e.g., *Salmonella typhimurium*, *Serratia*, e.g., *Serratia marcescens*, and *Shigella*, as well as *Bacilli* such as *B. subtilis* and *B. licheniformis* (e.g., *B. licheniformis* 41P disclosed in DD 266,710 published 12 April 1989), *Pseudomonas* such as *P. aeruginosa*, and *Streptomyces*. These examples are illustrative rather than limiting. Strain W3110 is one particularly preferred host or parent host because it is a common host strain for recombinant DNA product fermentations. Preferably, the host cell secretes minimal amounts of proteolytic enzymes. For example, strain W3110 may be modified to effect a genetic mutation in the genes encoding proteins endogenous to the host, with examples of such hosts including *E. coli* W3110 strain 1A2, which has the complete genotype *tonA*; *E. coli* W3110 strain 9E4, which has the complete genotype *tonA ptr3*; *E. coli* W3110 strain 27C7 (ATCC 55,244), which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT kan'*; *E. coli* W3110 strain 37D6, which has the complete genotype *tonA ptr3 phoA E15 (argF-lac)169 degP ompT rbs7 ilvG kan'*; *E. coli* W3110 strain 40B4, which is strain 37D6 with a non-kanamycin resistant *degP* deletion mutation; and an *E. coli* strain having mutant periplasmic protease disclosed in U.S. Patent No. 4,946,783 issued 7 August 1990. Alternatively, *in vitro* methods of cloning, e.g., PCR or other nucleic acid polymerase reactions, are suitable.

30 Full length antibody, antibody fragments, and antibody fusion proteins can be produced in bacteria, in particular when glycosylation and Fc effector function are not needed, such as when the therapeutic antibody is conjugated to a cytotoxic agent (e.g., a toxin) and the immunoconjugate by itself shows effectiveness in tumor cell destruction. Full length antibodies have greater half life in circulation. Production in *E. coli* is faster and more cost efficient. For expression of antibody fragments and polypeptides in bacteria, see, e.g., U.S. 5,648,237 (Carter et. al.), U.S. 5,789,199 (Joly et al.), and U.S. 5,840,523 (Simmons et al.) which describes translation initiation region (TIR) and signal sequences for optimizing expression and secretion, these patents incorporated herein by reference. After expression, the antibody is isolated from the *E. coli* cell paste in a soluble fraction and can be purified through, e.g., a protein A or G column depending on the isotype. Final purification can be carried out similar to the process for purifying antibody expressed e.g., in CHO cells.

In addition to prokaryotes, eukaryotic microbes such as filamentous fungi or yeast are suitable cloning or expression hosts for anti-TAT antibody- or TAT polypeptide-encoding vectors. *Saccharomyces cerevisiae* is a commonly used lower eukaryotic host microorganism. Others include *Schizosaccharomyces pombe* (Beach and Nurse, *Nature*, 290: 140 [1981]; EP 139,383 published 2 May 1985); *Kluyveromyces* hosts (U.S. Patent No. 4,943,529; Fleer et al., *Bio/Technology*, 9:968-975 (1991)) such as, e.g., *K. lactis* (MW98-8C, CBS683, CBS4574; Louvencourt et al., *J. Bacteriol.*, 154(2):737-742 [1983]), *K. fragilis* (ATCC 12,424), *K. bulgaricus* (ATCC 16,045), *K. wickeramii* (ATCC 24,178), *K. waltii* (ATCC 56,500), *K. drosophilicola* (ATCC 36,906; Van den Berg et al., *Bio/Technology*, 8:135 (1990)), *K. thermotolerans*, and *K. marxianus*; *Yarrowia* (EP 402,226); *Pichia pastoris* (EP 183,070; Sreekrishna et al., *J. Basic Microbiol.*, 28:265-278 [1988]); *Candida*; *Trichoderma reesii* (EP 244,234); *Neurospora crassa* (Case et al., *Proc. Natl. Acad. Sci. USA*, 76:5259-5263 [1979]); *Schwanniomyces* such as *Schwanniomyces occidentalis* (EP 394,538 published 31 October 1990); and filamentous fungi such as, e.g., *Neurospora*, *Penicillium*, *Tolypocladium* (WO 91/00357 published 10 January 1991), and *Aspergillus* hosts such as *A. nidulans* (Ballance et al., *Biochem. Biophys. Res. Commun.*, 112:284-289 [1983]; Tilburn et al., *Gene*, 26:205-221 [1983]; Yelton et al., *Proc. Natl. Acad. Sci. USA*, 81: 1470-1474 [1984]) and *A. niger* (Kelly and Hynes, *EMBO J.*, 4:475-479 [1985]). Methylotrophic yeasts are suitable herein and include, but are not limited to, yeast capable of growth on methanol selected from the genera consisting of *Hansenula*, *Candida*, *Kloeckera*, *Pichia*, *Saccharomyces*, *Torulopsis*, and *Rhodotorula*. A list of specific species that are exemplary of this class of yeasts may be found in C. Anthony, *The Biochemistry of Methylotrophs*, 269 (1982).

Suitable host cells for the expression of glycosylated anti-TAT antibody or TAT polypeptide are derived from multicellular organisms. Examples of invertebrate cells include insect cells such as *Drosophila* S2 and *Spodoptera* Sf9, as well as plant cells, such as cell cultures of cotton, corn, potato, soybean, petunia, tomato, and tobacco. Numerous baculoviral strains and variants and corresponding permissive insect host cells from hosts such as *Spodoptera frugiperda* (caterpillar), *Aedes aegypti* (mosquito), *Aedes albopictus* (mosquito), *Drosophila melanogaster* (fruitfly), and *Bombyx mori* have been identified. A variety of viral strains for transfection are publicly available, e.g., the L-1 variant of *Autographa californica* NPV and the Bm-5 strain of *Bombyx mori* NPV, and such viruses may be used as the virus herein according to the present invention, particularly for transfection of *Spodoptera frugiperda* cells.

However, interest has been greatest in vertebrate cells, and propagation of vertebrate cells in culture (tissue culture) has become a routine procedure. Examples of useful mammalian host cell lines are monkey kidney CV1 line transformed by SV40 (COS-7, ATCC CRL 1651); human embryonic kidney line (293 or 293 cells subcloned for growth in suspension culture, Graham et al., *J. Gen Virol.* 36:59 (1977)); baby hamster kidney cells (BHK, ATCC CCL 10); Chinese hamster ovary cells/-DHFR (CHO, Urlaub et al., *Proc. Natl. Acad. Sci. USA* 77:4216 (1980)); mouse sertoli cells (TM4, Mather, *Biol. Reprod.* 23:243-251 (1980)); monkey kidney cells (CV1 ATCC CCL 70); African green monkey kidney cells (VERO-76, ATCC CRL-1587); human cervical carcinoma cells (HELA, ATCC CCL 2); canine kidney cells (MDCK, ATCC CCL 34); buffalo rat liver cells (BRL 3A, ATCC CRL 1442); human lung cells (W138, ATCC CCL 75); human liver cells (Hep G2,

HB 8065); mouse mammary tumor (MMT 060562, ATCC CCL51); TRI cells (Mather et al., Annals N.Y. Acad. Sci. 383:44-68 (1982)); MRC 5 cells; FS4 cells; and a human hepatoma line (Hep G2).

Host cells are transformed with the above-described expression or cloning vectors for anti-TAT antibody or TAT polypeptide production and cultured in conventional nutrient media modified as appropriate for inducing promoters, selecting transformants, or amplifying the genes encoding the desired sequences.

5 3. Selection and Use of a Replicable Vector

The nucleic acid (e.g., cDNA or genomic DNA) encoding anti-TAT antibody or TAT polypeptide may be inserted into a replicable vector for cloning (amplification of the DNA) or for expression. Various vectors are publicly available. The vector may, for example, be in the form of a plasmid, cosmid, viral particle, or phage. The appropriate nucleic acid sequence may be inserted into the vector by a variety of procedures. In general, DNA is inserted into an appropriate restriction endonuclease site(s) using techniques known in the art. Vector components generally include, but are not limited to, one or more of a signal sequence, an origin of replication, one or more marker genes, an enhancer element, a promoter, and a transcription termination sequence. Construction of suitable vectors containing one or more of these components employs standard ligation techniques which are known to the skilled artisan.

15 The TAT may be produced recombinantly not only directly, but also as a fusion polypeptide with a heterologous polypeptide, which may be a signal sequence or other polypeptide having a specific cleavage site at the N-terminus of the mature protein or polypeptide. In general, the signal sequence may be a component of the vector, or it may be a part of the anti-TAT antibody- or TAT polypeptide-encoding DNA that is inserted into the vector. The signal sequence may be a prokaryotic signal sequence selected, for example, from the group of the alkaline phosphatase, penicillinase, lpp, or heat-stable enterotoxin II leaders. For yeast secretion the signal sequence may be, e.g., the yeast invertase leader, alpha factor leader (including *Saccharomyces* and *Kluyveromyces* α -factor leaders, the latter described in U.S. Patent No. 5,010,182), or acid phosphatase leader, the *C. albicans* glucoamylase leader (EP 362,179 published 4 April 1990), or the signal described in WO 90/13646 published 15 November 1990. In mammalian cell expression, mammalian signal sequences may be used to direct secretion of the protein, such as signal sequences from secreted polypeptides of the same or related species, as well as viral secretory leaders.

20 Both expression and cloning vectors contain a nucleic acid sequence that enables the vector to replicate in one or more selected host cells. Such sequences are well known for a variety of bacteria, yeast, and viruses. The origin of replication from the plasmid pBR322 is suitable for most Gram-negative bacteria, the 2μ plasmid origin is suitable for yeast, and various viral origins (SV40, polyoma, adenovirus, VSV or BPV) are useful for cloning vectors in mammalian cells.

25 Expression and cloning vectors will typically contain a selection gene, also termed a selectable marker. Typical selection genes encode proteins that (a) confer resistance to antibiotics or other toxins, e.g., ampicillin, neomycin, methotrexate, or tetracycline, (b) complement auxotrophic deficiencies, or (c) supply critical nutrients not available from complex media, e.g., the gene encoding D-alanine racemase for *Bacilli*.

30 An example of suitable selectable markers for mammalian cells are those that enable the identification

of cells competent to take up the anti-TAT antibody- or TAT polypeptide-encoding nucleic acid, such as DHFR or thymidine kinase. An appropriate host cell when wild-type DHFR is employed is the CHO cell line deficient in DHFR activity, prepared and propagated as described by Urlaub et al., Proc. Natl. Acad. Sci. USA, 77:4216 (1980). A suitable selection gene for use in yeast is the *trp1* gene present in the yeast plasmid YRp7 [Stinchcomb et al., Nature, 282:39 (1979); Kingsman et al., Gene, 7:141 (1979); Tschemper et al., Gene, 10:157 (1980)]. The *trp1* gene provides a selection marker for a mutant strain of yeast lacking the ability to grow in tryptophan, for example, ATCC No. 44076 or PEP4-1 [Jones, Genetics, 85:12 (1977)].

5 Expression and cloning vectors usually contain a promoter operably linked to the anti-TAT antibody- or TAT polypeptide-encoding nucleic acid sequence to direct mRNA synthesis. Promoters recognized by a variety of potential host cells are well known. Promoters suitable for use with prokaryotic hosts include the β -lactamase and lactose promoter systems [Chang et al., Nature, 275:615 (1978); Goeddel et al., Nature, 281:544 (1979)], alkaline phosphatase, a tryptophan (*trp*) promoter system [Goeddel, Nucleic Acids Res., 8:4057 (1980); EP 36,776], and hybrid promoters such as the tac promoter [deBoer et al., Proc. Natl. Acad. Sci. USA, 80:21-25 (1983)]. Promoters for use in bacterial systems also will contain a Shine-Dalgarno (S.D.) sequence operably linked to the DNA encoding anti-TAT antibody or TAT polypeptide.

10 Examples of suitable promoting sequences for use with yeast hosts include the promoters for 3-phosphoglycerate kinase [Hitzeman et al., J. Biol. Chem., 255:2073 (1980)] or other glycolytic enzymes [Hess et al., J. Adv. Enzyme Reg., 7:149 (1968); Holland, Biochemistry, 17:4900 (1978)], such as enolase, glyceraldehyde-3-phosphate dehydrogenase, hexokinase, pyruvate decarboxylase, phosphofructokinase, glucose-6-phosphate isomerase, 3-phosphoglycerate mutase, pyruvate kinase, triosephosphate isomerase, phosphoglucose isomerase, and glucokinase.

15 Other yeast promoters, which are inducible promoters having the additional advantage of transcription controlled by growth conditions, are the promoter regions for alcohol dehydrogenase 2, isocytchrome C, acid phosphatase, degradative enzymes associated with nitrogen metabolism, metallothionein, glyceraldehyde-3-phosphate dehydrogenase, and enzymes responsible for maltose and galactose utilization. Suitable vectors and promoters for use in yeast expression are further described in EP 73,657.

20 Anti-TAT antibody or TAT polypeptide transcription from vectors in mammalian host cells is controlled, for example, by promoters obtained from the genomes of viruses such as polyoma virus, fowlpox virus (UK 2,211,504 published 5 July 1989), adenovirus (such as Adenovirus 2), bovine papilloma virus, avian sarcoma virus, cytomegalovirus, a retrovirus, hepatitis-B virus and Simian Virus 40 (SV40), from heterologous mammalian promoters, e.g., the actin promoter or an immunoglobulin promoter, and from heat-shock promoters, provided such promoters are compatible with the host cell systems.

25 Transcription of a DNA encoding the anti-TAT antibody or TAT polypeptide by higher eukaryotes may be increased by inserting an enhancer sequence into the vector. Enhancers are *cis*-acting elements of DNA, usually about from 10 to 300 bp, that act on a promoter to increase its transcription. Many enhancer sequences are now known from mammalian genes (globin, elastase, albumin, α -fetoprotein, and insulin). Typically, however, one will use an enhancer from a eukaryotic cell virus. Examples include the SV40 enhancer on the

late side of the replication origin (bp 100-270), the cytomegalovirus early promoter enhancer, the polyoma enhancer on the late side of the replication origin, and adenovirus enhancers. The enhancer may be spliced into the vector at a position 5' or 3' to the anti-TAT antibody or TAT polypeptide coding sequence, but is preferably located at a site 5' from the promoter.

5 Expression vectors used in eukaryotic host cells (yeast, fungi, insect, plant, animal, human, or nucleated cells from other multicellular organisms) will also contain sequences necessary for the termination of transcription and for stabilizing the mRNA. Such sequences are commonly available from the 5' and, occasionally 3', untranslated regions of eukaryotic or viral DNAs or cDNAs. These regions contain nucleotide segments transcribed as polyadenylated fragments in the untranslated portion of the mRNA encoding anti-TAT antibody or TAT polypeptide.

10 Still other methods, vectors, and host cells suitable for adaptation to the synthesis of anti-TAT antibody or TAT polypeptide in recombinant vertebrate cell culture are described in Gething et al., *Nature*, 293:620-625 (1981); Mantei et al., *Nature*, 281:40-46 (1979); EP 117,060; and EP 117,058.

4. Culturing the Host Cells

15 The host cells used to produce the anti-TAT antibody or TAT polypeptide of this invention may be cultured in a variety of media. Commercially available media such as Ham's F10 (Sigma), Minimal Essential Medium ((MEM), (Sigma), RPMI-1640 (Sigma), and Dulbecco's Modified Eagle's Medium ((DMEM), Sigma) are suitable for culturing the host cells. In addition, any of the media described in Ham et al *Meth. Enz.* 58:44 (1979), Barnes et al., *Anal. Biochem.* 102:255 (1980), U.S. Pat. Nos. 4,767,704; 4,657,866; 4,927,762; 4,560,655; or 5,122,469; WO 90/03430; WO 87/00195; or U.S. Patent Re. 30,985 may be used as culture media for the host cells. Any of these media may be supplemented as necessary with hormones and/or other growth factors (such as insulin, transferrin, or epidermal growth factor), salts (such as sodium chloride, calcium, magnesium, and phosphate), buffers (such as HEPES), nucleotides (such as adenosine and thymidine), antibiotics (such as GENTAMYCIN™ drug), trace elements (defined as inorganic compounds usually present at final concentrations in the micromolar range), and glucose or an equivalent energy source. Any other necessary supplements may also be included at appropriate concentrations that would be known to those skilled in the art. The culture conditions, such as temperature, pH, and the like, are those previously used with the host cell selected for expression, and will be apparent to the ordinarily skilled artisan.

5. Detecting Gene Amplification/Expression

Gene amplification and/or expression may be measured in a sample directly, for example, by conventional Southern blotting, Northern blotting to quantitate the transcription of mRNA [Thomas, *Proc. Natl. Acad. Sci. USA*, 77:5201-5205 (1980)], dot blotting (DNA analysis), or *in situ* hybridization, using an appropriately labeled probe, based on the sequences provided herein. Alternatively, antibodies may be employed that can recognize specific duplexes, including DNA duplexes, RNA duplexes, and DNA-RNA hybrid duplexes or DNA-protein duplexes. The antibodies in turn may be labeled and the assay may be carried out where the duplex is bound to a surface, so that upon the formation of duplex on the surface, the presence of antibody bound to the duplex can be detected.

Gene expression, alternatively, may be measured by immunological methods, such as immunohistochemical staining of cells or tissue sections and assay of cell culture or body fluids, to quantitate directly the expression of gene product. Antibodies useful for immunohistochemical staining and/or assay of sample fluids may be either monoclonal or polyclonal, and may be prepared in any mammal. Conveniently, the antibodies may be prepared against a native sequence TAT polypeptide or against a synthetic peptide based on the DNA sequences provided herein or against exogenous sequence fused to TAT DNA and encoding a specific antibody epitope.

10 6. Purification of Anti-TAT Antibody and TAT Polypeptide

Forms of anti-TAT antibody and TAT polypeptide may be recovered from culture medium or from host cell lysates. If membrane-bound, it can be released from the membrane using a suitable detergent solution (e.g. Triton-X 100) or by enzymatic cleavage. Cells employed in expression of anti-TAT antibody and TAT polypeptide can be disrupted by various physical or chemical means, such as freeze-thaw cycling, sonication, 15 mechanical disruption, or cell lysing agents.

It may be desired to purify anti-TAT antibody and TAT polypeptide from recombinant cell proteins or polypeptides. The following procedures are exemplary of suitable purification procedures: by fractionation on an ion-exchange column; ethanol precipitation; reverse phase HPLC; chromatography on silica or on a cation-exchange resin such as DEAE; chromatofocusing; SDS-PAGE; ammonium sulfate precipitation; gel filtration using, for example, Sephadex G-75; protein A Sepharose columns to remove contaminants such as IgG; and metal chelating columns to bind epitope-tagged forms of the anti-TAT antibody and TAT polypeptide. Various methods of protein purification may be employed and such methods are known in the art and described for example in Deutscher, *Methods in Enzymology*, 182 (1990); Scopes, *Protein Purification: Principles and Practice*, Springer-Verlag, New York (1982). The purification step(s) selected will depend, for example, on the nature of the production process used and the particular anti-TAT antibody or TAT polypeptide produced.

30 When using recombinant techniques, the antibody can be produced intracellularly, in the periplasmic space, or directly secreted into the medium. If the antibody is produced intracellularly, as a first step, the particulate debris, either host cells or lysed fragments, are removed, for example, by centrifugation or ultrafiltration. Carter et al., *Bio/Technology* 10:163-167 (1992) describe a procedure for isolating antibodies 35 which are secreted to the periplasmic space of *E. coli*. Briefly, cell paste is thawed in the presence of sodium

acetate (pH 3.5), EDTA, and phenylmethylsulfonylfluoride (PMSF) over about 30 min. Cell debris can be removed by centrifugation. Where the antibody is secreted into the medium, supernatants from such expression systems are generally first concentrated using a commercially available protein concentration filter, for example, an Amicon or Millipore Pellicon ultrafiltration unit. A protease inhibitor such as PMSF may be included in any of the foregoing steps to inhibit proteolysis and antibiotics may be included to prevent the growth of adventitious 5 contaminants.

The antibody composition prepared from the cells can be purified using, for example, hydroxylapatite chromatography, gel electrophoresis, dialysis, and affinity chromatography, with affinity chromatography being the preferred purification technique. The suitability of protein A as an affinity ligand depends on the species and isotype of any immunoglobulin Fc domain that is present in the antibody. Protein A can be used to purify 10 antibodies that are based on human γ 1, γ 2 or γ 4 heavy chains (Lindmark et al., *J. Immunol. Meth.* 62:1-13 (1983)). Protein G is recommended for all mouse isotypes and for human γ 3 (Guss et al., *EMBO J.* 5:1567-1575 (1986)). The matrix to which the affinity ligand is attached is most often agarose, but other 15 matrices are available. Mechanically stable matrices such as controlled pore glass or poly(styrene divinyl)benzene allow for faster flow rates and shorter processing times than can be achieved with agarose. Where the antibody comprises a C_h3 domain, the Bakerbond ABX™ resin (J. T. Baker, Phillipsburg, NJ) is useful for purification. Other techniques for protein purification such as fractionation on an ion-exchange column, ethanol precipitation, Reverse Phase HPLC, chromatography on silica, chromatography on heparin 20 SEPHAROSE™ chromatography on an anion or cation exchange resin (such as a polyaspartic acid column), chromatofocusing, SDS-PAGE, and ammonium sulfate precipitation are also available depending on the antibody to be recovered.

Following any preliminary purification step(s), the mixture comprising the antibody of interest and contaminants may be subjected to low pH hydrophobic interaction chromatography using an elution buffer at a pH between about 2.5-4.5, preferably performed at low salt concentrations (e.g., from about 0-0.25M salt).

J. Pharmaceutical Formulations

Therapeutic formulations of the anti-TAT antibodies, TAT binding oligopeptides, TAT binding organic molecules and/or TAT polypeptides used in accordance with the present invention are prepared for storage by mixing the antibody, polypeptide, oligopeptide or organic molecule having the desired degree of purity with optional pharmaceutically acceptable carriers, excipients or stabilizers (*Remington's Pharmaceutical Sciences* 16th edition, Osol, A. Ed. (1980)), in the form of lyophilized formulations or aqueous solutions. Acceptable carriers, excipients, or stabilizers are nontoxic to recipients at the dosages and concentrations employed, and include buffers such as acetate, Tris, phosphate, citrate, and other organic acids; antioxidants including ascorbic acid and methionine; preservatives (such as octadecyl dimethylbenzyl ammonium chloride; hexamethonium chloride; benzalkonium chloride, benzethonium chloride; phenol, butyl or benzyl alcohol; alkyl parabens such as methyl or propyl paraben; catechol; resorcinol; cyclohexanol; 3-pentanol; and m-cresol); low molecular weight (less than about 10 residues) polypeptides; proteins, such as serum albumin, gelatin, or immunoglobulins; 25 hydrophilic polymers such as polyvinylpyrrolidone; amino acids such as glycine, glutamine, asparagine, 30 35

histidine, arginine, or lysine; monosaccharides, disaccharides, and other carbohydrates including glucose, mannose, or dextrans; chelating agents such as EDTA; tonicifiers such as trehalose and sodium chloride; sugars such as sucrose, mannitol, trehalose or sorbitol; surfactant such as polysorbate; salt-forming counter-ions such as sodium; metal complexes (e.g., Zn-protein complexes); and/or non-ionic surfactants such as TWEEN®, PLURONICS® or polyethylene glycol (PEG). The antibody preferably comprises the antibody at a 5 concentration of between 5-200 mg/ml, preferably between 10-100 mg/ml.

The formulations herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. For example, in addition to an anti-TAT antibody, TAT binding oligopeptide, or TAT binding organic molecule, it may be desirable to include in the one formulation, an additional antibody, e.g., a second 10 anti-TAT antibody which binds a different epitope on the TAT polypeptide, or an antibody to some other target such as a growth factor that affects the growth of the particular cancer. Alternatively, or additionally, the composition may further comprise a chemotherapeutic agent, cytotoxic agent, cytokine, growth inhibitory agent, anti-hormonal agent, and/or cardioprotectant. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

15 The active ingredients may also be entrapped in microcapsules prepared, for example, by coacervation techniques or by interfacial polymerization, for example, hydroxymethylcellulose or gelatin-microcapsules and poly-(methylmethacrylate) microcapsules, respectively, in colloidal drug delivery systems (for example, liposomes, albumin microspheres, microemulsions, nano-particles and nanocapsules) or in macroemulsions. Such techniques are disclosed in Remington's Pharmaceutical Sciences, 16th edition, Osol, A. Ed. (1980).

20 Sustained-release preparations may be prepared. Suitable examples of sustained-release preparations include semi-permeable matrices of solid hydrophobic polymers containing the antibody, which matrices are in the form of shaped articles, e.g., films, or microcapsules. Examples of sustained-release matrices include polyesters, hydrogels (for example, poly(2-hydroxyethyl-methacrylate), or poly(vinylalcohol)), polylactides (U.S. Pat. No. 3,773,919), copolymers of L-glutamic acid and γ ethyl-L-glutamate, non-degradable ethylene-vinyl acetate, degradable lactic acid-glycolic acid copolymers such as the LUPRON DEPOT® (injectable 25 microspheres composed of lactic acid-glycolic acid copolymer and leuprolide acetate), and poly-D-(-)-3-hydroxybutyric acid.

The formulations to be used for *in vivo* administration must be sterile. This is readily accomplished by filtration through sterile filtration membranes.

30 **K. Diagnosis and Treatment with Anti-TAT Antibodies, TAT Binding Oligopeptides and TAT Binding Organic Molecules**

To determine TAT expression in the cancer, various diagnostic assays are available. In one embodiment, TAT polypeptide overexpression may be analyzed by immunohistochemistry (IHC). Paraffin embedded tissue sections from a tumor biopsy may be subjected to the IHC assay and accorded a TAT protein 35 staining intensity criteria as follows:

Score 0 - no staining is observed or membrane staining is observed in less than 10% of tumor cells.

Score 1+ - a faint/barely perceptible membrane staining is detected in more than 10% of the tumor cells. The cells are only stained in part of their membrane.

Score 2+ - a weak to moderate complete membrane staining is observed in more than 10% of the tumor cells.

5 Score 3+ - a moderate to strong complete membrane staining is observed in more than 10% of the tumor cells.

Those tumors with 0 or 1+ scores for TAT polypeptide expression may be characterized as not overexpressing TAT, whereas those tumors with 2+ or 3+ scores may be characterized as overexpressing TAT.

10 Alternatively, or additionally, FISH assays such as the INFORM® (sold by Ventana, Arizona) or PATHVISION® (Vysis, Illinois) may be carried out on formalin-fixed, paraffin-embedded tumor tissue to determine the extent (if any) of TAT overexpression in the tumor.

15 TAT overexpression or amplification may be evaluated using an *in vivo* diagnostic assay, e.g., by administering a molecule (such as an antibody, oligopeptide or organic molecule) which binds the molecule to be detected and is tagged with a detectable label (e.g., a radioactive isotope or a fluorescent label) and externally scanning the patient for localization of the label.

20 As described above, the anti-TAT antibodies, oligopeptides and organic molecules of the invention have various non-therapeutic applications. The anti-TAT antibodies, oligopeptides and organic molecules of the present invention can be useful for diagnosis and staging of TAT polypeptide-expressing cancers (e.g., in radioimaging). The antibodies, oligopeptides and organic molecules are also useful for purification or 25 immunoprecipitation of TAT polypeptide from cells, for detection and quantitation of TAT polypeptide *in vitro*, e.g., in an ELISA or a Western blot, to kill and eliminate TAT-expressing cells from a population of mixed cells as a step in the purification of other cells.

Currently, depending on the stage of the cancer, cancer treatment involves one or a combination of the 25 following therapies: surgery to remove the cancerous tissue, radiation therapy, and chemotherapy. Anti-TAT antibody, oligopeptide or organic molecule therapy may be especially desirable in elderly patients who do not tolerate the toxicity and side effects of chemotherapy well and in metastatic disease where radiation therapy has limited usefulness. The tumor targeting anti-TAT antibodies, oligopeptides and organic molecules of the invention are useful to alleviate TAT-expressing cancers upon initial diagnosis of the disease or during relapse. 30 For therapeutic applications, the anti-TAT antibody, oligopeptide or organic molecule can be used alone, or in combination therapy with, e.g., hormones, antiangiogens, or radiolabelled compounds, or with surgery, cryotherapy, and/or radiotherapy. Anti-TAT antibody, oligopeptide or organic molecule treatment can be administered in conjunction with other forms of conventional therapy, either consecutively with, pre- or post-conventional therapy. Chemotherapeutic drugs such as TAXOTERE® (docetaxel), TAXOL® (paclitaxel), 35 estramustine and mitoxantrone are used in treating cancer, in particular, in good risk patients. In the present method of the invention for treating or alleviating cancer, the cancer patient can be administered anti-TAT

antibody, oligopeptide or organic molecule in conjunction with treatment with the one or more of the preceding chemotherapeutic agents. In particular, combination therapy with paclitaxel and modified derivatives (see, e.g., EP0600517) is contemplated. The anti-TAT antibody, oligopeptide or organic molecule will be administered with a therapeutically effective dose of the chemotherapeutic agent. In another embodiment, the anti-TAT antibody, oligopeptide or organic molecule is administered in conjunction with chemotherapy to enhance the 5 activity and efficacy of the chemotherapeutic agent, e.g., paclitaxel. The Physicians' Desk Reference (PDR) discloses dosages of these agents that have been used in treatment of various cancers. The dosing regimen and dosages of these aforementioned chemotherapeutic drugs that are therapeutically effective will depend on the particular cancer being treated, the extent of the disease and other factors familiar to the physician of skill in the art and can be determined by the physician.

10 In one particular embodiment, a conjugate comprising an anti-TAT antibody, oligopeptide or organic molecule conjugated with a cytotoxic agent is administered to the patient. Preferably, the immunoconjugate bound to the TAT protein is internalized by the cell, resulting in increased therapeutic efficacy of the immunoconjugate in killing the cancer cell to which it binds. In a preferred embodiment, the cytotoxic agent targets or interferes with the nucleic acid in the cancer cell. Examples of such cytotoxic agents are described 15 above and include maytansinoids, calicheamicins, ribonucleases and DNA endonucleases.

20 The anti-TAT antibodies, oligopeptides, organic molecules or toxin conjugates thereof are administered to a human patient, in accord with known methods, such as intravenous administration, e.g., as a bolus or by continuous infusion over a period of time, by intramuscular, intraperitoneal, intracerebrospinal, subcutaneous, intra-articular, intrasynovial, intrathecal, oral, topical, or inhalation routes. Intravenous or subcutaneous administration of the antibody, oligopeptide or organic molecule is preferred.

25 Other therapeutic regimens may be combined with the administration of the anti-TAT antibody, oligopeptide or organic molecule. The combined administration includes co-administration, using separate formulations or a single pharmaceutical formulation, and consecutive administration in either order, wherein preferably there is a time period while both (or all) active agents simultaneously exert their biological activities. Preferably such combined therapy results in a synergistic therapeutic effect.

30 It may also be desirable to combine administration of the anti-TAT antibody or antibodies, oligopeptides or organic molecules, with administration of an antibody directed against another tumor antigen associated with the particular cancer.

35 In another embodiment, the therapeutic treatment methods of the present invention involves the combined administration of an anti-TAT antibody (or antibodies), oligopeptides or organic molecules and one or more chemotherapeutic agents or growth inhibitory agents, including co-administration of cocktails of different chemotherapeutic agents. Chemotherapeutic agents include estramustine phosphate, prednimustine, cisplatin, 5-fluorouracil, melphalan, cyclophosphamide, hydroxyurea and hydroxyureataxanes (such as paclitaxel and doxetaxel) and/or anthracycline antibiotics. Preparation and dosing schedules for such chemotherapeutic agents may be used according to manufacturers' instructions or as determined empirically by the skilled practitioner. Preparation and dosing schedules for such chemotherapy are also described in *Chemotherapy*

Service Ed., M.C. Perry, Williams & Wilkins, Baltimore, MD (1992).

The antibody, oligopeptide or organic molecule may be combined with an anti-hormonal compound; e.g., an anti-estrogen compound such as tamoxifen; an anti-progesterone such as onapristone (see, EP 616 812); or an anti-androgen such as flutamide, in dosages known for such molecules. Where the cancer to be treated is androgen independent cancer, the patient may previously have been subjected to anti-androgen therapy and, after the cancer becomes androgen independent, the anti-TAT antibody, oligopeptide or organic molecule (and optionally other agents as described herein) may be administered to the patient.

Sometimes, it may be beneficial to also co-administer a cardioprotectant (to prevent or reduce myocardial dysfunction associated with the therapy) or one or more cytokines to the patient. In addition to the above therapeutic regimes, the patient may be subjected to surgical removal of cancer cells and/or radiation therapy, before, simultaneously with, or post antibody, oligopeptide or organic molecule therapy. Suitable dosages for any of the above co-administered agents are those presently used and may be lowered due to the combined action (synergy) of the agent and anti-TAT antibody, oligopeptide or organic molecule.

For the prevention or treatment of disease, the dosage and mode of administration will be chosen by the physician according to known criteria. The appropriate dosage of antibody, oligopeptide or organic molecule will depend on the type of disease to be treated, as defined above, the severity and course of the disease, whether the antibody, oligopeptide or organic molecule is administered for preventive or therapeutic purposes, previous therapy, the patient's clinical history and response to the antibody, oligopeptide or organic molecule, and the discretion of the attending physician. The antibody, oligopeptide or organic molecule is suitably administered to the patient at one time or over a series of treatments. Preferably, the antibody, oligopeptide or organic molecule is administered by intravenous infusion or by subcutaneous injections. Depending on the type and severity of the disease, about 1 μ g/kg to about 50 mg/kg body weight (e.g., about 0.1-15mg/kg/dose) of antibody can be an initial candidate dosage for administration to the patient, whether, for example, by one or more separate administrations, or by continuous infusion. A dosing regimen can comprise administering an initial loading dose of about 4 mg/kg, followed by a weekly maintenance dose of about 2 mg/kg of the anti-TAT antibody. However, other dosage regimens may be useful. A typical daily dosage might range from about 1 μ g/kg to 100 mg/kg or more, depending on the factors mentioned above. For repeated administrations over several days or longer, depending on the condition, the treatment is sustained until a desired suppression of disease symptoms occurs. The progress of this therapy can be readily monitored by conventional methods and assays and based on criteria known to the physician or other persons of skill in the art.

Aside from administration of the antibody protein to the patient, the present application contemplates administration of the antibody by gene therapy. Such administration of nucleic acid encoding the antibody is encompassed by the expression "administering a therapeutically effective amount of an antibody". See, for example, WO96/07321 published March 14, 1996 concerning the use of gene therapy to generate intracellular antibodies.

There are two major approaches to getting the nucleic acid (optionally contained in a vector) into the patient's cells; *in vivo* and *ex vivo*. For *in vivo* delivery the nucleic acid is injected directly into the patient,

usually at the site where the antibody is required. For *ex vivo* treatment, the patient's cells are removed, the nucleic acid is introduced into these isolated cells and the modified cells are administered to the patient either directly or, for example, encapsulated within porous membranes which are implanted into the patient (see, e.g., U.S. Patent Nos. 4,892,538 and 5,283,187). There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. A commonly used vector for *ex vivo* delivery of the gene is a retroviral vector.

5 The currently preferred *in vivo* nucleic acid transfer techniques include transfection with viral vectors (such as adenovirus, Herpes simplex I virus, or adeno-associated virus) and lipid-based systems (useful lipids for lipid-mediated transfer of the gene are DOTMA, DOPE and DC-Chol, for example). For review of the currently known gene marking and gene therapy protocols see Anderson et al., *Science* 256:808-813 (1992). See also WO 93/25673 and the references cited therein.

10 The anti-TAT antibodies of the invention can be in the different forms encompassed by the definition of "antibody" herein. Thus, the antibodies include full length or intact antibody, antibody fragments, native sequence antibody or amino acid variants, humanized, chimeric or fusion antibodies, immunoconjugates, and functional fragments thereof. In fusion antibodies an antibody sequence is fused to a heterologous polypeptide sequence. The antibodies can be modified in the Fc region to provide desired effector functions. As discussed 15 in more detail in the sections herein, with the appropriate Fc regions, the naked antibody bound on the cell surface can induce cytotoxicity, e.g., via antibody-dependent cellular cytotoxicity (ADCC) or by recruiting complement in complement dependent cytotoxicity, or some other mechanism. Alternatively, where it is desirable to eliminate or reduce effector function, so as to minimize side effects or therapeutic complications, 20 certain other Fc regions may be used.

25 In one embodiment, the antibody competes for binding or bind substantially to, the same epitope as the antibodies of the invention. Antibodies having the biological characteristics of the present anti-TAT antibodies of the invention are also contemplated, specifically including the *in vivo* tumor targeting and any cell proliferation inhibition or cytotoxic characteristics.

Methods of producing the above antibodies are described in detail herein.

30 The present anti-TAT antibodies, oligopeptides and organic molecules are useful for treating a TAT-expressing cancer or alleviating one or more symptoms of the cancer in a mammal. Such a cancer includes prostate cancer, cancer of the urinary tract, lung cancer, breast cancer, colon cancer and ovarian cancer, more 35 specifically, prostate adenocarcinoma, renal cell carcinomas, colorectal adenocarcinomas, lung adenocarcinomas, lung squamous cell carcinomas, and pleural mesothelioma. The cancers encompass metastatic cancers of any of the preceding. The antibody, oligopeptide or organic molecule is able to bind to at least a portion of the cancer cells that express TAT polypeptide in the mammal. In a preferred embodiment, the antibody, oligopeptide or organic molecule is effective to destroy or kill TAT-expressing tumor cells or inhibit

the growth of such tumor cells, *in vitro* or *in vivo*, upon binding to TAT polypeptide on the cell. Such an antibody includes a naked anti-TAT antibody (not conjugated to any agent). Naked antibodies that have cytotoxic or cell growth inhibition properties can be further harnessed with a cytotoxic agent to render them even more potent in tumor cell destruction. Cytotoxic properties can be conferred to an anti-TAT antibody by, e.g., conjugating the antibody with a cytotoxic agent, to form an immunoconjugate as described herein. The 5 cytotoxic agent or a growth inhibitory agent is preferably a small molecule. Toxins such as calicheamicin or a maytansinoid and analogs or derivatives thereof, are preferable.

The invention provides a composition comprising an anti-TAT antibody, oligopeptide or organic molecule of the invention, and a carrier. For the purposes of treating cancer, compositions can be administered to the patient in need of such treatment, wherein the composition can comprise one or more anti-TAT antibodies 10 present as an immunoconjugate or as the naked antibody. In a further embodiment, the compositions can comprise these antibodies, oligopeptides or organic molecules in combination with other therapeutic agents such as cytotoxic or growth inhibitory agents, including chemotherapeutic agents. The invention also provides formulations comprising an anti-TAT antibody, oligopeptide or organic molecule of the invention, and a carrier. In one embodiment, the formulation is a therapeutic formulation comprising a pharmaceutically acceptable 15 carrier.

Another aspect of the invention is isolated nucleic acids encoding the anti-TAT antibodies. Nucleic acids encoding both the H and L chains and especially the hypervariable region residues, chains which encode the native sequence antibody as well as variants, modifications and humanized versions of the antibody, are encompassed.

20 The invention also provides methods useful for treating a TAT polypeptide-expressing cancer or alleviating one or more symptoms of the cancer in a mammal, comprising administering a therapeutically effective amount of an anti-TAT antibody, oligopeptide or organic molecule to the mammal. The antibody, oligopeptide or organic molecule therapeutic compositions can be administered short term (acute) or chronic, or intermittent as directed by physician. Also provided are methods of inhibiting the growth of, and killing a 25 TAT polypeptide-expressing cell.

The invention also provides kits and articles of manufacture comprising at least one anti-TAT antibody, oligopeptide or organic molecule. Kits containing anti-TAT antibodies, oligopeptides or organic molecules find use, e.g., for TAT cell killing assays, for purification or immunoprecipitation of TAT polypeptide from cells. For example, for isolation and purification of TAT, the kit can contain an anti-TAT antibody, oligopeptide or 30 organic molecule coupled to beads (e.g., sepharose beads). Kits can be provided which contain the antibodies, oligopeptides or organic molecules for detection and quantitation of TAT *in vitro*, e.g., in an ELISA or a Western blot. Such antibody, oligopeptide or organic molecule useful for detection may be provided with a label such as a fluorescent or radiolabel.

L. Articles of Manufacture and Kits

35 Another embodiment of the invention is an article of manufacture containing materials useful for the treatment of anti-TAT expressing cancer. The article of manufacture comprises a container and a label or

package insert on or associated with the container. Suitable containers include, for example, bottles, vials, syringes, etc. The containers may be formed from a variety of materials such as glass or plastic. The container holds a composition which is effective for treating the cancer condition and may have a sterile access port (for example the container may be an intravenous solution bag or a vial having a stopper pierceable by a hypodermic injection needle). At least one active agent in the composition is an anti-TAT antibody, oligopeptide or organic molecule of the invention. The label or package insert indicates that the composition is used for treating cancer. The label or package insert will further comprise instructions for administering the antibody, oligopeptide or organic molecule composition to the cancer patient. Additionally, the article of manufacture may further comprise a second container comprising a pharmaceutically-acceptable buffer, such as bacteriostatic water for injection (BWFI), phosphate-buffered saline, Ringer's solution and dextrose solution. It may further include other materials desirable from a commercial and user standpoint, including other buffers, diluents, filters, needles, and syringes.

Kits are also provided that are useful for various purposes, e.g., for TAT-expressing cell killing assays, for purification or immunoprecipitation of TAT polypeptide from cells. For isolation and purification of TAT polypeptide, the kit can contain an anti-TAT antibody, oligopeptide or organic molecule coupled to beads (e.g., sepharose beads). Kits can be provided which contain the antibodies, oligopeptides or organic molecules for detection and quantitation of TAT polypeptide *in vitro*, e.g., in an ELISA or a Western blot. As with the article of manufacture, the kit comprises a container and a label or package insert on or associated with the container. The container holds a composition comprising at least one anti-TAT antibody, oligopeptide or organic molecule of the invention. Additional containers may be included that contain, e.g., diluents and buffers, control antibodies. The label or package insert may provide a description of the composition as well as instructions for the intended *in vitro* or diagnostic use.

M. Uses for TAT Polypeptides and TAT-Polypeptide Encoding Nucleic Acids

Nucleotide sequences (or their complement) encoding TAT polypeptides have various applications in the art of molecular biology, including uses as hybridization probes, in chromosome and gene mapping and in the generation of anti-sense RNA and DNA probes. TAT-encoding nucleic acid will also be useful for the preparation of TAT polypeptides by the recombinant techniques described herein, wherein those TAT polypeptides may find use, for example, in the preparation of anti-TAT antibodies as described herein.

The full-length native sequence TAT gene, or portions thereof, may be used as hybridization probes for a cDNA library to isolate the full-length TAT cDNA or to isolate still other cDNAs (for instance, those encoding naturally-occurring variants of TAT or TAT from other species) which have a desired sequence identity to the native TAT sequence disclosed herein. Optionally, the length of the probes will be about 20 to about 50 bases. The hybridization probes may be derived from at least partially novel regions of the full length native nucleotide sequence wherein those regions may be determined without undue experimentation or from genomic sequences including promoters, enhancer elements and introns of native sequence TAT. By way of example, a screening method will comprise isolating the coding region of the TAT gene using the known DNA sequence to synthesize a selected probe of about 40 bases. Hybridization probes may be labeled by a variety

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of labels, including radionucleotides such as ^{32}P or ^{35}S , or enzymatic labels such as alkaline phosphatase coupled to the probe via avidin/biotin coupling systems. Labeled probes having a sequence complementary to that of the TAT gene of the present invention can be used to screen libraries of human cDNA, genomic DNA or mRNA to determine which members of such libraries the probe hybridizes to. Hybridization techniques are described in further detail in the Examples below. Any EST sequences disclosed in the present application may similarly be employed as probes, using the methods disclosed herein.

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Other useful fragments of the TAT-encoding nucleic acids include antisense or sense oligonucleotides comprising a single-stranded nucleic acid sequence (either RNA or DNA) capable of binding to target TAT mRNA (sense) or TAT DNA (antisense) sequences. Antisense or sense oligonucleotides, according to the present invention, comprise a fragment of the coding region of TAT DNA. Such a fragment generally comprises at least about 14 nucleotides, preferably from about 14 to 30 nucleotides. The ability to derive an antisense or a sense oligonucleotide, based upon a cDNA sequence encoding a given protein is described in, for example, Stein and Cohen (*Cancer Res.* 48:2659, 1988) and van der Krol et al. (*BioTechniques* 6:958, 1988).

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Binding of antisense or sense oligonucleotides to target nucleic acid sequences results in the formation of duplexes that block transcription or translation of the target sequence by one of several means, including enhanced degradation of the duplexes, premature termination of transcription or translation, or by other means. Such methods are encompassed by the present invention. The antisense oligonucleotides thus may be used to block expression of TAT proteins, wherein those TAT proteins may play a role in the induction of cancer in mammals. Antisense or sense oligonucleotides further comprise oligonucleotides having modified sugar-phosphodiester backbones (or other sugar linkages, such as those described in WO 91/06629) and wherein such sugar linkages are resistant to endogenous nucleases. Such oligonucleotides with resistant sugar linkages are stable *in vivo* (i.e., capable of resisting enzymatic degradation) but retain sequence specificity to be able to bind to target nucleotide sequences.

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Preferred intragenic sites for antisense binding include the region incorporating the translation initiation/start codon (5'-AUG / 5'-ATG) or termination/stop codon (5'-UAA, 5'-UAG and 5'-UGA / 5'-TAA, 5'-TAG and 5'-TGA) of the open reading frame (ORF) of the gene. These regions refer to a portion of the mRNA or gene that encompasses from about 25 to about 50 contiguous nucleotides in either direction (i.e., 5' or 3') from a translation initiation or termination codon. Other preferred regions for antisense binding include: introns; exons; intron-exon junctions; the open reading frame (ORF) or "coding region," which is the region between the translation initiation codon and the translation termination codon; the 5' cap of an mRNA which comprises an N7-methylated guanosine residue joined to the 5'-most residue of the mRNA via a 5'-5' triphosphate linkage and includes 5' cap structure itself as well as the first 50 nucleotides adjacent to the cap; the 5' untranslated region (5'UTR), the portion of an mRNA in the 5' direction from the translation initiation codon, and thus including nucleotides between the 5' cap site and the translation initiation codon of an mRNA or corresponding nucleotides on the gene; and the 3' untranslated region (3'UTR), the portion of an mRNA in the 3' direction from the translation termination codon, and thus including nucleotides between the translation termination codon and 3' end of an mRNA or corresponding nucleotides on the gene.

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Specific examples of preferred antisense compounds useful for inhibiting expression of TAT proteins include oligonucleotides containing modified backbones or non-natural internucleoside linkages. Oligonucleotides having modified backbones include those that retain a phosphorus atom in the backbone and those that do not have a phosphorus atom in the backbone. For the purposes of this specification, and as sometimes referenced in the art, modified oligonucleotides that do not have a phosphorus atom in their internucleoside backbone can 5 also be considered to be oligonucleosides. Preferred modified oligonucleotide backbones include, for example, phosphorothioates, chiral phosphorothioates, phosphorodithioates, phosphotriesters, aminoalkylphosphotri-esters, methyl and other alkyl phosphonates including 3'-alkylene phosphonates, 5'-alkylene phosphonates and chiral phosphonates, phosphinates, phosphoramidates including 3'-amino phosphoramidate and 10 aminoalkylphosphoramidates, thionophosphoramidates, thionoalkylphosphonates, thionoalkylphosphotriesters, selenophosphates and borano-phosphates having normal 3'-5' linkages, 2'-5' linked analogs of these, and those having inverted polarity wherein one or more internucleotide linkages is a 3' to 3', 5' to 5' or 2' to 2' linkage. Preferred oligonucleotides having inverted polarity comprise a single 3' to 3' linkage at the 3'-most 15 internucleotide linkage i.e. a single inverted nucleoside residue which may be abasic (the nucleobase is missing or has a hydroxyl group in place thereof). Various salts, mixed salts and free acid forms are also included. Representative United States patents that teach the preparation of phosphorus-containing linkages include, but are not limited to, U.S. Pat. Nos.: 3,687,808; 4,469,863; 4,476,301; 5,023,243; 5,177,196; 5,188,897; 5,264,423; 5,276,019; 5,278,302; 5,286,717; 5,321,131; 5,399,676; 5,405,939; 5,453,496; 5,455,233; 5,466,677; 5,476,925; 5,519,126; 5,536,821; 5,541,306; 5,550,111; 5,563,253; 5,571,799; 5,587,361; 5,194,599; 5,565,555; 5,527,899; 5,721,218; 5,672,697 and 5,625,050, each of which is herein incorporated 20 by reference.

Preferred modified oligonucleotide backbones that do not include a phosphorus atom therein have backbones that are formed by short chain alkyl or cycloalkyl internucleoside linkages, mixed heteroatom and alkyl or cycloalkyl internucleoside linkages, or one or more short chain heteroatomic or heterocyclic internucleoside linkages. These include those having morpholino linkages (formed in part from the sugar portion 25 of a nucleoside); siloxane backbones; sulfide, sulfoxide and sulfone backbones; formacetyl and thioformacetyl backbones; methylene formacetyl and thioformacetyl backbones; riboacetyl backbones; alkene containing backbones; sulfamate backbones; methyleneimino and methylenehydrazino backbones; sulfonate and sulfonamide backbones; amide backbones; and others having mixed N, O, S and CH₂ component parts. Representative United States patents that teach the preparation of such oligonucleosides include, but are not limited to, U.S. Pat. Nos.: 5,034,506; 5,166,315; 5,185,444; 5,214,134; 5,216,141; 5,235,033; 5,264,562; 5,264,564; 5,405,938; 5,434,257; 5,466,677; 5,470,967; 5,489,677; 5,541,307; 5,561,225; 5,596,086; 5,602,240; 5,610,289; 5,602,240; 5,608,046; 5,610,289; 5,618,704; 5,623,070; 5,663,312; 5,633,360; 5,677,437; 5,792,608; 5,646,269 and 5,677,439, each of which is herein incorporated by reference.

In other preferred antisense oligonucleotides, both the sugar and the internucleoside linkage, i.e., the 35 backbone, of the nucleotide units are replaced with novel groups. The base units are maintained for hybridization with an appropriate nucleic acid target compound. One such oligomeric compound, an oligonucleotide mimetic

that has been shown to have excellent hybridization properties, is referred to as a peptide nucleic acid (PNA). In PNA compounds, the sugar-backbone of an oligonucleotide is replaced with an amide containing backbone, in particular an aminoethylglycine backbone. The nucleobases are retained and are bound directly or indirectly to aza nitrogen atoms of the amide portion of the backbone. Representative United States patents that teach the preparation of PNA compounds include, but are not limited to, U.S. Pat. Nos.: 5,539,082; 5,714,331; and 5,719,262, each of which is herein incorporated by reference. Further teaching of PNA compounds can be found in Nielsen et al., *Science*, 1991, 254, 1497-1500.

Preferred antisense oligonucleotides incorporate phosphorothioate backbones and/or heteroatom backbones, and in particular -CH₂-NH-O-CH₂-, -CH₂-N(CH₃)-O-CH₂- [known as a methylene (methylimino) or MMI backbone], -CH₂-O-N(CH₃)-CH₂-, -CH₂-N(CH₃)-N(CH₃)-CH₂- and -O-N(CH₃)-CH₂-CH₂- [wherein the native phosphodiester backbone is represented as -O-P-O-CH₂] described in the above referenced U.S. Pat. No. 5,489,677, and the amide backbones of the above referenced U.S. Pat. No. 5,602,240. Also preferred are antisense oligonucleotides having morpholino backbone structures of the above-referenced U.S. Pat. No. 5,034,506.

Modified oligonucleotides may also contain one or more substituted sugar moieties. Preferred oligonucleotides comprise one of the following at the 2' position: OH; F; O-alkyl, S-alkyl, or N-alkyl; O-alkenyl, S-alkenyl, or N-alkenyl; O-alkynyl, S-alkynyl or N-alkynyl; or O-alkyl-O-alkyl, wherein the alkyl, alkenyl and alkynyl may be substituted or unsubstituted C₁ to C₁₀ alkyl or C₂ to C₁₀ alkenyl and alkynyl. Particularly preferred are O[(CH₂)_nO]_mCH₃, O(CH₂)_nOCH₃, O(CH₂)_nNH₂, O(CH₂)_nCH₃, O(CH₂)_nONH₂, and O(CH₂)_nON[(CH₂)_nCH₃]₂, where n and m are from 1 to about 10. Other preferred antisense oligonucleotides comprise one of the following at the 2' position: C₁ to C₁₀ lower alkyl, substituted lower alkyl, alkenyl, alkynyl, alkaryl, aralkyl, O-alkaryl or O-aralkyl, SH, SCH₃, OCN, Cl, Br, CN, CF₃, OCF₃, SOCH₃, SO₂CH₃, ONO₂, NO₂, N₃, NH₂, heterocycloalkyl, heterocycloalkaryl, aminoalkylamino, polyalkylamino, substituted silyl, an RNA cleaving group, a reporter group, an intercalator, a group for improving the pharmacokinetic properties of an oligonucleotide, or a group for improving the pharmacodynamic properties of an oligonucleotide, and other substituents having similar properties. A preferred modification includes 2'-methoxyethoxy (2'-O-CH₂CH₂OCH₃, also known as 2'-O-(2-methoxyethyl) or 2'-MOE) (Martin et al., *Helv. Chim. Acta*, 1995, 78, 486-504) i.e., an alkoxyalkoxy group. A further preferred modification includes 2'-dimethylaminoxyethoxy, i.e., a O(CH₂)₂ON(CH₃)₂ group, also known as 2'-DMAOE, as described in examples hereinbelow, and 2'-dimethylaminoethoxyethoxy (also known in the art as 2'-O-dimethylaminoethoxyethyl or 2'-DMAEOE), i.e., 2'-O-CH₂-O-CH₂-N(CH₃)₂.

A further preferred modification includes Locked Nucleic Acids (LNAs) in which the 2'-hydroxyl group is linked to the 3' or 4' carbon atom of the sugar ring thereby forming a bicyclic sugar moiety. The linkage is preferably a methylene (-CH₂)_n group bridging the 2' oxygen atom and the 4' carbon atom wherein n is 1 or 2. LNAs and preparation thereof are described in WO 98/39352 and WO 99/14226.

Other preferred modifications include 2'-methoxy (2'-O-CH₃), 2'-aminopropoxy (2'-OCH₂CH₂CH₂NH₂)

NH₂), 2'-allyl (2'-CH₂-CH=CH₂), 2'-O-allyl (2'-O-CH₂-CH=CH₂) and 2'-fluoro (2'-F). The 2'-modification may be in the arabino (up) position or ribo (down) position. A preferred 2'-arabino modification is 2'-F. Similar modifications may also be made at other positions on the oligonucleotide, particularly the 3' position of the sugar on the 3' terminal nucleotide or in 2'-5' linked oligonucleotides and the 5' position of 5' terminal nucleotide. Oligonucleotides may also have sugar mimetics such as cyclobutyl moieties in place of the pentofuranosyl sugar.

5 Representative United States patents that teach the preparation of such modified sugar structures include, but are not limited to, U.S. Pat. Nos.: 4,981,957; 5,118,800; 5,319,080; 5,359,044; 5,393,878; 5,446,137; 5,466,786; 5,514,785; 5,519,134; 5,567,811; 5,576,427; 5,591,722; 5,597,909; 5,610,300; 5,627,053; 5,639,873; 5,646,265; 5,658,873; 5,670,633; 5,792,747; and 5,700,920, each of which is herein incorporated by reference in its entirety.

10 Oligonucleotides may also include nucleobase (often referred to in the art simply as "base") modifications or substitutions. As used herein, "unmodified" or "natural" nucleobases include the purine bases adenine (A) and guanine (G), and the pyrimidine bases thymine (T), cytosine (C) and uracil (U). Modified nucleobases include other synthetic and natural nucleobases such as 5-methylcytosine (5-me-C), 5-hydroxymethyl cytosine, xanthine, hypoxanthine, 2-aminoadenine, 6-methyl and other alkyl derivatives of adenine and guanine, 2-propyl and other alkyl derivatives of adenine and guanine, 2-thiouracil, 2-thiothymine and 2-thiocytosine, 5-halouracil and cytosine, 5-propynyl (-C≡C-CH₃ or -CH₂-C≡CH) uracil and cytosine and other alkynyl derivatives of pyrimidine bases, 6-azo uracil, cytosine and thymine, 5-uracil (pseudouracil), 4-thiouracil, 8-halo, 8-amino, 8-thiol, 8-thioalkyl, 8-hydroxyl and other 8-substituted adenines and guanines, 5-halo particularly 5-bromo, 5-trifluoromethyl and other 5-substituted uracils and cytosines, 7-methylguanine and 7-methyladenine, 2-F-adenine, 2-amino-adenine, 8-azaguanine and 8-azaadenine, 7-deazaguanine and 7-deazaadenine and 3-deazaguanine and 3-deazaadenine. Further modified nucleobases include tricyclic pyrimidines such as phenoxazine cytidine(1H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), phenothiazine cytidine (1H-pyrimido[5,4-b][1,4]benzothiazin-2(3H)-one), G-clamps such as a substituted phenoxazine cytidine (e.g. 9-(2-aminoethoxy)-H-pyrimido[5,4-b][1,4]benzoxazin-2(3H)-one), carbazole cytidine (2H-pyrimido[4,5-b]indol-2-one), pyridoindole cytidine (H-pyrido[3',2':4,5]pyrrolo[2,3-d]pyrimidin-2-one). Modified nucleobases may also include those in which the purine or pyrimidine base is replaced with other heterocycles, for example 7-deaza-adenine, 7-deazaguanosine, 2-aminopyridine and 2-pyridone. Further nucleobases include those disclosed in U.S. Pat. No. 3,687,808, those disclosed in The Concise Encyclopedia Of Polymer Science And Engineering, pages 858-859, Kroschwitz, J. I., ed. John Wiley & Sons, 1990, and those disclosed by Englisch et al., Angewandte Chemie, International Edition, 1991, 30, 613. Certain of these nucleobases are particularly useful for increasing the binding affinity of the oligomeric compounds of the invention. These include 5-substituted pyrimidines, 6-azapyrimidines and N-2, N-6 and O-6 substituted purines, including 2-aminopropyladenine, 5-propynyluracil and 5-propynylcytosine. 5-methylcytosine substitutions have been shown to increase nucleic acid duplex stability by 0.6-1.2.degree. C. (Sanghvi et al, Antisense Research and Applications, CRC Press, Boca Raton, 1993, pp. 276-278) and are preferred base substitutions, even more particularly when combined with 2'-O-methoxyethyl sugar modifications. Representative United States patents

that teach the preparation of modified nucleobases include, but are not limited to: U.S. Pat. No. 3,687,808, as well as U.S. Pat. Nos.: 4,845,205; 5,130,302; 5,134,066; 5,175,273; 5,367,066; 5,432,272; 5,457,187; 5,459,255; 5,484,908; 5,502,177; 5,525,711; 5,552,540; 5,587,469; 5,594,121, 5,596,091; 5,614,617; 5,645,985; 5,830,653; 5,763,588; 6,005,096; 5,681,941 and 5,750,692, each of which is herein incorporated by reference.

5 Another modification of antisense oligonucleotides chemically linking to the oligonucleotide one or more moieties or conjugates which enhance the activity, cellular distribution or cellular uptake of the oligonucleotide. The compounds of the invention can include conjugate groups covalently bound to functional groups such as primary or secondary hydroxyl groups. Conjugate groups of the invention include intercalators, reporter molecules, polyamines, polyamides, polyethylene glycols, polyethers, groups that enhance the pharmacodynamic properties of oligomers, and groups that enhance the pharmacokinetic properties of oligomers. Typical conjugates groups include cholesterol, lipids, cation lipids, phospholipids, cationic phospholipids, biotin, phenazine, folate, phenanthridine, anthraquinone, acridine, fluoresceins, rhodamines, coumarins, and dyes. Groups that enhance the pharmacodynamic properties, in the context of this invention, include groups that improve oligomer uptake, enhance oligomer resistance to degradation, and/or strengthen 10 sequence-specific hybridization with RNA. Groups that enhance the pharmacokinetic properties, in the context of this invention, include groups that improve oligomer uptake, distribution, metabolism or excretion. Conjugate moieties include but are not limited to lipid moieties such as a cholesterol moiety (Letsinger et al., Proc. Natl. Acad. Sci. USA, 1989, 86, 6553-6556), cholic acid (Manoharan et al., Bioorg. Med. Chem. Lett., 1994, 4, 1053-1060), a thioether, e.g., hexyl-S-tritylthiol (Manoharan et al., Ann. N. Y. Acad. Sci., 1992, 660, 306-309; 15 Manoharan et al., Bioorg. Med. Chem. Lett., 1993, 3, 2765-2770), a thiocholesterol (Oberhauser et al., Nucl. Acids Res., 1992, 20, 533-538), an aliphatic chain, e.g., dodecandiol or undecyl residues (Saison-Behmoaras et al., EMBO J., 1991, 10, 1111-1118; Kabanov et al., FEBS Lett., 1990, 259, 327-330; Svinarchuk et al., Biochimie, 1993, 75, 49-54), a phospholipid, e.g., di-hexadecyl-rac-glycerol or triethyl-ammonium 1,2-di-O-hexadecyl-rac-glycero-3-H-phosphonate (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654; 20 Shea et al., Nucl. Acids Res., 1990, 18, 3777-3783), a polyamine or a polyethylene glycol chain (Manoharan et al., Nucleosides & Nucleotides, 1995, 14, 969-973), or adamantane acetic acid (Manoharan et al., Tetrahedron Lett., 1995, 36, 3651-3654), a palmityl moiety (Mishra et al., Biochim. Biophys. Acta, 1995, 1264, 229-237), or an octadecylamine or hexylamino-carbonyl-oxycholesterol moiety. Oligonucleotides of the 25 invention may also be conjugated to active drug substances, for example, aspirin, warfarin, phenylbutazone, ibuprofen, suprofen, fenbufen, ketoprofen, (S)-(+)-pranoprofen, carprofen, dansylsarcosine, 2,3,5-triiodobenzoic acid, flufenamic acid, folinic acid, a benzothiadiazide, chlorothiazide, a diazepine, indomethicin, a barbiturate, a cephalosporin, a sulfa drug, an antidiabetic, an antibacterial or an antibiotic. Oligonucleotide-drug conjugates and their preparation are described in U.S. patent application Ser. No. 09/334,130 (filed Jun. 15, 1999) and United States patents Nos.: 4,828,979; 4,948,882; 5,218,105; 5,525,465; 30 5,541,313; 5,545,730; 5,552,538; 5,578,717, 5,580,731; 5,580,731; 5,591,584; 5,109,124; 5,118,802; 5,138,045; 5,414,077; 5,486,603; 5,512,439; 5,578,718; 5,608,046; 4,587,044; 4,605,735; 4,667,025;

4,762,779; 4,789,737; 4,824,941; 4,835,263; 4,876,335; 4,904,582; 4,958,013; 5,082,830; 5,112,963; 5,214,136; 5,082,830; 5,112,963; 5,214,136; 5,245,022; 5,254,469; 5,258,506; 5,262,536; 5,272,250; 5,292,873; 5,317,098; 5,371,241, 5,391,723; 5,416,203, 5,451,463; 5,510,475; 5,512,667; 5,514,785; 5,565,552; 5,567,810; 5,574,142; 5,585,481; 5,587,371; 5,595,726; 5,597,696; 5,599,923; 5,599,928 and 5,688,941, each of which is herein incorporated by reference.

5 It is not necessary for all positions in a given compound to be uniformly modified, and in fact more than one of the aforementioned modifications may be incorporated in a single compound or even at a single nucleoside within an oligonucleotide. The present invention also includes antisense compounds which are chimeric compounds. "Chimeric" antisense compounds or "chimeras," in the context of this invention, are antisense compounds, particularly oligonucleotides, which contain two or more chemically distinct regions, each made up of at least one monomer unit, i.e., a nucleotide in the case of an oligonucleotide compound. These oligonucleotides typically contain at least one region wherein the oligonucleotide is modified so as to confer upon the oligonucleotide increased resistance to nuclease degradation, increased cellular uptake, and/or increased binding affinity for the target nucleic acid. An additional region of the oligonucleotide may serve as a substrate for enzymes capable of cleaving RNA:DNA or RNA:RNA hybrids. By way of example, RNase H is a cellular 10 endonuclease which cleaves the RNA strand of an RNA:DNA duplex. Activation of RNase H, therefore, results in cleavage of the RNA target, thereby greatly enhancing the efficiency of oligonucleotide inhibition of gene expression. Consequently, comparable results can often be obtained with shorter oligonucleotides when chimeric oligonucleotides are used, compared to phosphorothioate deoxyoligonucleotides hybridizing to the same target 15 region. Chimeric antisense compounds of the invention may be formed as composite structures of two or more oligonucleotides, modified oligonucleotides, oligonucleosides and/or oligonucleotide mimetics as described above. Preferred chimeric antisense oligonucleotides incorporate at least one 2' modified sugar (preferably 2'-O-(CH₂)₂-O-CH₃) at the 3' terminal to confer nuclease resistance and a region with at least 4 contiguous 2'-H sugars to confer RNase H activity. Such compounds have also been referred to in the art as hybrids or gapmers. Preferred gapmers have a region of 2' modified sugars (preferably 2'-O-(CH₂)₂-O-CH₃) at the 3'-terminal and 20 at the 5' terminal separated by at least one region having at least 4 contiguous 2'-H sugars and preferably incorporate phosphorothioate backbone linkages. Representative United States patents that teach the preparation of such hybrid structures include, but are not limited to, U.S. Pat. Nos. 5,013,830; 5,149,797; 5,220,007; 5,256,775; 5,366,878; 5,403,711; 5,491,133; 5,565,350; 5,623,065; 5,652,355; 5,652,356; and 5,700,922, 25 each of which is herein incorporated by reference in its entirety.

30 The antisense compounds used in accordance with this invention may be conveniently and routinely made through the well-known technique of solid phase synthesis. Equipment for such synthesis is sold by several vendors including, for example, Applied Biosystems (Foster City, Calif.). Any other means for such synthesis known in the art may additionally or alternatively be employed. It is well known to use similar techniques to prepare oligonucleotides such as the phosphorothioates and alkylated derivatives. The compounds 35 of the invention may also be admixed, encapsulated, conjugated or otherwise associated with other molecules, molecule structures or mixtures of compounds, as for example, liposomes, receptor targeted molecules, oral,

rectal, topical or other formulations, for assisting in uptake, distribution and/or absorption. Representative United States patents that teach the preparation of such uptake, distribution and/or absorption assisting formulations include, but are not limited to, U.S. Pat. Nos. 5,108,921; 5,354,844; 5,416,016; 5,459,127; 5,521,291; 5,543,158; 5,547,932; 5,583,020; 5,591,721; 4,426,330; 4,534,899; 5,013,556; 5,108,921; 5,213,804; 5,227,170; 5,264,221; 5,356,633; 5,395,619; 5,416,016; 5,417,978; 5,462,854; 5,469,854; 5,512,295; 5,527,528; 5,534,259; 5,543,152; 5,556,948; 5,580,575; and 5,595,756, each of which is herein incorporated by reference.

Other examples of sense or antisense oligonucleotides include those oligonucleotides which are covalently linked to organic moieties, such as those described in WO 90/10048, and other moieties that increases affinity of the oligonucleotide for a target nucleic acid sequence, such as poly-(L-lysine). Further still, intercalating agents, such as ellipticine, and alkylating agents or metal complexes may be attached to sense or antisense oligonucleotides to modify binding specificities of the antisense or sense oligonucleotide for the target nucleotide sequence.

Antisense or sense oligonucleotides may be introduced into a cell containing the target nucleic acid sequence by any gene transfer method, including, for example, CaPO_4 -mediated DNA transfection, 10 electroporation, or by using gene transfer vectors such as Epstein-Barr virus. In a preferred procedure, an antisense or sense oligonucleotide is inserted into a suitable retroviral vector. A cell containing the target nucleic acid sequence is contacted with the recombinant retroviral vector, either *in vivo* or *ex vivo*. Suitable retroviral vectors include, but are not limited to, those derived from the murine retrovirus M-MuLV, N2 (a retrovirus derived from M-MuLV), or the double copy vectors designated DCT5A, DCT5B and DCT5C (see 15 WO 90/13641).

Sense or antisense oligonucleotides also may be introduced into a cell containing the target nucleotide sequence by formation of a conjugate with a ligand binding molecule, as described in WO 91/04753. Suitable ligand binding molecules include, but are not limited to, cell surface receptors, growth factors, other cytokines, or other ligands that bind to cell surface receptors. Preferably, conjugation of the ligand binding molecule does 20 not substantially interfere with the ability of the ligand binding molecule to bind to its corresponding molecule or receptor, or block entry of the sense or antisense oligonucleotide or its conjugated version into the cell.

Alternatively, a sense or an antisense oligonucleotide may be introduced into a cell containing the target nucleic acid sequence by formation of an oligonucleotide-lipid complex, as described in WO 90/10448. The sense or antisense oligonucleotide-lipid complex is preferably dissociated within the cell by an endogenous 30 lipase.

Antisense or sense RNA or DNA molecules are generally at least about 5 nucleotides in length, alternatively at least about 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 35, 40, 45, 50, 55, 60, 65, 70, 75, 80, 85, 90, 95, 100, 105, 110, 115, 120, 125, 130, 135, 140, 145, 150, 155, 160, 165, 170, 175, 180, 185, 190, 195, 200, 210, 220, 230, 240, 250, 260, 270, 280, 290, 300, 310, 320, 330, 340, 350, 360, 370, 380, 390, 400, 410, 420, 430, 440, 450, 460, 470, 480, 490, 500, 510, 520, 530, 540, 550, 560, 570, 580, 590, 600, 610, 620, 630, 640, 650, 660, 670, 680, 690, 700, 710,

720, 730, 740, 750, 760, 770, 780, 790, 800, 810, 820, 830, 840, 850, 860, 870, 880, 890, 900, 910, 920, 930, 940, 950, 960, 970, 980, 990, or 1000 nucleotides in length, wherein in this context the term "about" means the referenced nucleotide sequence length plus or minus 10% of that referenced length.

The probes may also be employed in PCR techniques to generate a pool of sequences for identification of closely related TAT coding sequences.

5 Nucleotide sequences encoding a TAT can also be used to construct hybridization probes for mapping the gene which encodes that TAT and for the genetic analysis of individuals with genetic disorders. The nucleotide sequences provided herein may be mapped to a chromosome and specific regions of a chromosome using known techniques, such as *in situ* hybridization, linkage analysis against known chromosomal markers, and hybridization screening with libraries.

10 When the coding sequences for TAT encode a protein which binds to another protein (example, where the TAT is a receptor), the TAT can be used in assays to identify the other proteins or molecules involved in the binding interaction. By such methods, inhibitors of the receptor/ligand binding interaction can be identified. Proteins involved in such binding interactions can also be used to screen for peptide or small molecule inhibitors or agonists of the binding interaction. Also, the receptor TAT can be used to isolate correlative ligand(s).
15 Screening assays can be designed to find lead compounds that mimic the biological activity of a native TAT or a receptor for TAT. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates. Small molecules contemplated include synthetic organic or inorganic compounds. The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays and 20 cell based assays, which are well characterized in the art.

Nucleic acids which encode TAT or its modified forms can also be used to generate either transgenic animals or "knock out" animals which, in turn, are useful in the development and screening of therapeutically useful reagents. A transgenic animal (e.g., a mouse or rat) is an animal having cells that contain a transgene, which transgene was introduced into the animal or an ancestor of the animal at a prenatal, e.g., an embryonic 25 stage. A transgene is a DNA which is integrated into the genome of a cell from which a transgenic animal develops. In one embodiment, cDNA encoding TAT can be used to clone genomic DNA encoding TAT in accordance with established techniques and the genomic sequences used to generate transgenic animals that contain cells which express DNA encoding TAT. Methods for generating transgenic animals, particularly animals such as mice or rats, have become conventional in the art and are described, for example, in U.S. 30 Patent Nos. 4,736,866 and 4,870,009. Typically, particular cells would be targeted for TAT transgene incorporation with tissue-specific enhancers. Transgenic animals that include a copy of a transgene encoding TAT introduced into the germ line of the animal at an embryonic stage can be used to examine the effect of increased expression of DNA encoding TAT. Such animals can be used as tester animals for reagents thought to confer protection from, for example, pathological conditions associated with its overexpression. In 35 accordance with this facet of the invention, an animal is treated with the reagent and a reduced incidence of the pathological condition, compared to untreated animals bearing the transgene, would indicate a potential

therapeutic intervention for the pathological condition.

Alternatively, non-human homologues of TAT can be used to construct a TAT "knock out" animal which has a defective or altered gene encoding TAT as a result of homologous recombination between the endogenous gene encoding TAT and altered genomic DNA encoding TAT introduced into an embryonic stem cell of the animal. For example, cDNA encoding TAT can be used to clone genomic DNA encoding TAT in accordance with established techniques. A portion of the genomic DNA encoding TAT can be deleted or replaced with another gene, such as a gene encoding a selectable marker which can be used to monitor integration. Typically, several kilobases of unaltered flanking DNA (both at the 5' and 3' ends) are included in the vector [see e.g., Thomas and Capecchi, *Cell*, 51:503 (1987) for a description of homologous recombination vectors]. The vector is introduced into an embryonic stem cell line (e.g., by electroporation) and cells in which the introduced DNA has homologously recombined with the endogenous DNA are selected [see e.g., Li et al., *Cell*, 69:915 (1992)]. The selected cells are then injected into a blastocyst of an animal (e.g., a mouse or rat) to form aggregation chimeras [see e.g., Bradley, in *Teratocarcinomas and Embryonic Stem Cells: A Practical Approach*, E. J. Robertson, ed. (IRL, Oxford, 1987), pp. 113-152]. A chimeric embryo can then be implanted into a suitable pseudopregnant female foster animal and the embryo brought to term to create a "knock out" animal. Progeny harboring the homologously recombined DNA in their germ cells can be identified by standard techniques and used to breed animals in which all cells of the animal contain the homologously recombined DNA. Knockout animals can be characterized for instance, for their ability to defend against certain pathological conditions and for their development of pathological conditions due to absence of the TAT polypeptide.

Nucleic acid encoding the TAT polypeptides may also be used in gene therapy. In gene therapy applications, genes are introduced into cells in order to achieve *in vivo* synthesis of a therapeutically effective genetic product, for example for replacement of a defective gene. "Gene therapy" includes both conventional gene therapy where a lasting effect is achieved by a single treatment, and the administration of gene therapeutic agents, which involves the one time or repeated administration of a therapeutically effective DNA or mRNA. Antisense RNAs and DNAs can be used as therapeutic agents for blocking the expression of certain genes *in vivo*. It has already been shown that short antisense oligonucleotides can be imported into cells where they act as inhibitors, despite their low intracellular concentrations caused by their restricted uptake by the cell membrane. (Zamecnik et al., *Proc. Natl. Acad. Sci. USA* 83:4143-4146 [1986]). The oligonucleotides can be modified to enhance their uptake, e.g. by substituting their negatively charged phosphodiester groups by uncharged groups.

There are a variety of techniques available for introducing nucleic acids into viable cells. The techniques vary depending upon whether the nucleic acid is transferred into cultured cells *in vitro*, or *in vivo* in the cells of the intended host. Techniques suitable for the transfer of nucleic acid into mammalian cells *in vitro* include the use of liposomes, electroporation, microinjection, cell fusion, DEAE-dextran, the calcium phosphate precipitation method, etc. The currently preferred *in vivo* gene transfer techniques include transfection with viral (typically retroviral) vectors and viral coat protein-liposome mediated transfection (Dzau

et al., Trends in Biotechnology 11, 205-210 [1993]). In some situations it is desirable to provide the nucleic acid source with an agent that targets the target cells, such as an antibody specific for a cell surface membrane protein or the target cell, a ligand for a receptor on the target cell, etc. Where liposomes are employed, proteins which bind to a cell surface membrane protein associated with endocytosis may be used for targeting and/or to facilitate uptake, e.g. capsid proteins or fragments thereof tropic for a particular cell type, antibodies for proteins which undergo internalization in cycling, proteins that target intracellular localization and enhance intracellular half-life. The technique of receptor-mediated endocytosis is described, for example, by Wu et al., J. Biol. Chem. 262, 4429-4432 (1987); and Wagner et al., Proc. Natl. Acad. Sci. USA 87, 3410-3414 (1990). For review of gene marking and gene therapy protocols see Anderson et al., Science 256, 808-813 (1992).

5 The nucleic acid molecules encoding the TAT polypeptides or fragments thereof described herein are useful for chromosome identification. In this regard, there exists an ongoing need to identify new chromosome markers, since relatively few chromosome marking reagents, based upon actual sequence data are presently available. Each TAT nucleic acid molecule of the present invention can be used as a chromosome marker.

10 The TAT polypeptides and nucleic acid molecules of the present invention may also be used diagnostically for tissue typing, wherein the TAT polypeptides of the present invention may be differentially expressed in one tissue as compared to another, preferably in a diseased tissue as compared to a normal tissue 15 of the same tissue type. TAT nucleic acid molecules will find use for generating probes for PCR, Northern analysis, Southern analysis and Western analysis.

15 This invention encompasses methods of screening compounds to identify those that mimic the TAT polypeptide (agonists) or prevent the effect of the TAT polypeptide (antagonists). Screening assays for 20 antagonist drug candidates are designed to identify compounds that bind or complex with the TAT polypeptides encoded by the genes identified herein, or otherwise interfere with the interaction of the encoded polypeptides with other cellular proteins, including e.g., inhibiting the expression of TAT polypeptide from cells. Such screening assays will include assays amenable to high-throughput screening of chemical libraries, making them particularly suitable for identifying small molecule drug candidates.

25 The assays can be performed in a variety of formats, including protein-protein binding assays, biochemical screening assays, immunoassays, and cell-based assays, which are well characterized in the art.

All assays for antagonists are common in that they call for contacting the drug candidate with a TAT 30 polypeptide encoded by a nucleic acid identified herein under conditions and for a time sufficient to allow these two components to interact.

In binding assays, the interaction is binding and the complex formed can be isolated or detected in the reaction mixture. In a particular embodiment, the TAT polypeptide encoded by the gene identified herein or the drug candidate is immobilized on a solid phase, e.g., on a microtiter plate, by covalent or non-covalent 35 attachments. Non-covalent attachment generally is accomplished by coating the solid surface with a solution of the TAT polypeptide and drying. Alternatively, an immobilized antibody, e.g., a monoclonal antibody, specific for the TAT polypeptide to be immobilized can be used to anchor it to a solid surface. The assay is performed by adding the non-immobilized component, which may be labeled by a detectable label, to the

immobilized component, e.g., the coated surface containing the anchored component. When the reaction is complete, the non-reacted components are removed, e.g., by washing, and complexes anchored on the solid surface are detected. When the originally non-immobilized component carries a detectable label, the detection of label immobilized on the surface indicates that complexing occurred. Where the originally non-immobilized component does not carry a label, complexing can be detected, for example, by using a labeled antibody 5 specifically binding the immobilized complex.

If the candidate compound interacts with but does not bind to a particular TAT polypeptide encoded by a gene identified herein, its interaction with that polypeptide can be assayed by methods well known for detecting protein-protein interactions. Such assays include traditional approaches, such as, e.g., cross-linking, co-immunoprecipitation, and co-purification through gradients or chromatographic columns. In addition, 10 protein-protein interactions can be monitored by using a yeast-based genetic system described by Fields and co-workers (Fields and Song, Nature (London), 340:245-246 (1989); Chien et al., Proc. Natl. Acad. Sci. USA, 88:9578-9582 (1991)) as disclosed by Chevray and Nathans, Proc. Natl. Acad. Sci. USA, 89: 5789-5793 (1991). Many transcriptional activators, such as yeast GAL4, consist of two physically discrete modular 15 domains, one acting as the DNA-binding domain, the other one functioning as the transcription-activation domain. The yeast expression system described in the foregoing publications (generally referred to as the "two-hybrid system") takes advantage of this property, and employs two hybrid proteins, one in which the target protein is fused to the DNA-binding domain of GAL4, and another, in which candidate activating proteins are fused to the activation domain. The expression of a GAL1- lacZ reporter gene under control of a GAL4-activated promoter depends on reconstitution of GAL4 activity via protein-protein interaction. Colonies 20 containing interacting polypeptides are detected with a chromogenic substrate for β -galactosidase. A complete kit (MATCHMAKERTM) for identifying protein-protein interactions between two specific proteins using the two-hybrid technique is commercially available from Clontech. This system can also be extended to map protein domains involved in specific protein interactions as well as to pinpoint amino acid residues that are crucial for 25 these interactions.

Compounds that interfere with the interaction of a gene encoding a TAT polypeptide identified herein and other intra- or extracellular components can be tested as follows: usually a reaction mixture is prepared containing the product of the gene and the intra- or extracellular component under conditions and for a time allowing for the interaction and binding of the two products. To test the ability of a candidate compound to inhibit binding, the reaction is run in the absence and in the presence of the test compound. In addition, a 30 placebo may be added to a third reaction mixture, to serve as positive control. The binding (complex formation) between the test compound and the intra- or extracellular component present in the mixture is monitored as described hereinabove. The formation of a complex in the control reaction(s) but not in the reaction mixture containing the test compound indicates that the test compound interferes with the interaction of the test compound and its reaction partner.

To assay for antagonists, the TAT polypeptide may be added to a cell along with the compound to be 35 screened for a particular activity and the ability of the compound to inhibit the activity of interest in the presence

of the TAT polypeptide indicates that the compound is an antagonist to the TAT polypeptide. Alternatively, antagonists may be detected by combining the TAT polypeptide and a potential antagonist with membrane-bound TAT polypeptide receptors or recombinant receptors under appropriate conditions for a competitive inhibition assay. The TAT polypeptide can be labeled, such as by radioactivity, such that the number of TAT polypeptide molecules bound to the receptor can be used to determine the effectiveness of the potential antagonist. The gene encoding the receptor can be identified by numerous methods known to those of skill in the art, for example, 5 ligand panning and FACS sorting. Coligan et al., Current Protocols in Immun., 1(2): Chapter 5 (1991). Preferably, expression cloning is employed wherein polyadenylated RNA is prepared from a cell responsive to the TAT polypeptide and a cDNA library created from this RNA is divided into pools and used to transfect COS cells or other cells that are not responsive to the TAT polypeptide. Transfected cells that are grown on glass 10 slides are exposed to labeled TAT polypeptide. The TAT polypeptide can be labeled by a variety of means including iodination or inclusion of a recognition site for a site-specific protein kinase. Following fixation and incubation, the slides are subjected to autoradiographic analysis. Positive pools are identified and sub-pools are prepared and re-transfected using an interactive sub-pooling and re-screening process, eventually yielding a 15 single clone that encodes the putative receptor.

15 As an alternative approach for receptor identification, labeled TAT polypeptide can be photoaffinity-linked with cell membrane or extract preparations that express the receptor molecule. Cross-linked material is resolved by PAGE and exposed to X-ray film. The labeled complex containing the receptor can be excised, 20 resolved into peptide fragments, and subjected to protein micro-sequencing. The amino acid sequence obtained from micro- sequencing would be used to design a set of degenerate oligonucleotide probes to screen a cDNA library to identify the gene encoding the putative receptor.

In another assay for antagonists, mammalian cells or a membrane preparation expressing the receptor would be incubated with labeled TAT polypeptide in the presence of the candidate compound. The ability of 25 the compound to enhance or block this interaction could then be measured.

More specific examples of potential antagonists include an oligonucleotide that binds to the fusions of 30 immunoglobulin with TAT polypeptide, and, in particular, antibodies including, without limitation, poly- and monoclonal antibodies and antibody fragments, single-chain antibodies, anti-idiotypic antibodies, and chimeric or humanized versions of such antibodies or fragments, as well as human antibodies and antibody fragments. Alternatively, a potential antagonist may be a closely related protein, for example, a mutated form of the TAT 35 polypeptide that recognizes the receptor but imparts no effect, thereby competitively inhibiting the action of the TAT polypeptide.

Another potential TAT polypeptide antagonist is an antisense RNA or DNA construct prepared using 35 antisense technology, where, e.g., an antisense RNA or DNA molecule acts to block directly the translation of mRNA by hybridizing to targeted mRNA and preventing protein translation. Antisense technology can be used to control gene expression through triple-helix formation or antisense DNA or RNA, both of which methods are based on binding of a polynucleotide to DNA or RNA. For example, the 5' coding portion of the 40 polynucleotide sequence, which encodes the mature TAT polypeptides herein, is used to design an antisense

RNA oligonucleotide of from about 10 to 40 base pairs in length. A DNA oligonucleotide is designed to be complementary to a region of the gene involved in transcription (triple helix - see Lee et al., Nucl. Acids Res., 6:3073 (1979); Cooney et al., Science, 241: 456 (1988); Dervan et al., Science, 251:1360 (1991)), thereby preventing transcription and the production of the TAT polypeptide. The antisense RNA oligonucleotide hybridizes to the mRNA *in vivo* and blocks translation of the mRNA molecule into the TAT polypeptide (antisense - Okano, Neurochem., 56:560 (1991); Oligodeoxynucleotides as Antisense Inhibitors of Gene Expression (CRC Press: Boca Raton, FL, 1988). The oligonucleotides described above can also be delivered to cells such that the antisense RNA or DNA may be expressed *in vivo* to inhibit production of the TAT polypeptide. When antisense DNA is used, oligodeoxyribonucleotides derived from the translation-initiation site, e.g., between about -10 and +10 positions of the target gene nucleotide sequence, are preferred.

Potential antagonists include small molecules that bind to the active site, the receptor binding site, or growth factor or other relevant binding site of the TAT polypeptide, thereby blocking the normal biological activity of the TAT polypeptide. Examples of small molecules include, but are not limited to, small peptides or peptide-like molecules, preferably soluble peptides, and synthetic non-peptidyl organic or inorganic compounds.

Ribozymes are enzymatic RNA molecules capable of catalyzing the specific cleavage of RNA. Ribozymes act by sequence-specific hybridization to the complementary target RNA, followed by endonucleolytic cleavage. Specific ribozyme cleavage sites within a potential RNA target can be identified by known techniques. For further details see, e.g., Ross Current Biology, 4:469-471 (1994), and PCT publication No. WO 97/33551 (published September 18, 1997).

Nucleic acid molecules in triple-helix formation used to inhibit transcription should be single-stranded and composed of deoxynucleotides. The base composition of these oligonucleotides is designed such that it promotes triple-helix formation via Hoogsteen base-pairing rules, which generally require sizeable stretches of purines or pyrimidines on one strand of a duplex. For further details see, e.g., PCT publication No. WO 97/33551, *supra*.

These small molecules can be identified by any one or more of the screening assays discussed hereinabove and/or by any other screening techniques well known for those skilled in the art.

Isolated TAT polypeptide-encoding nucleic acid can be used herein for recombinantly producing TAT polypeptide using techniques well known in the art and as described herein. In turn, the produced TAT polypeptides can be employed for generating anti-TAT antibodies using techniques well known in the art and as described herein.

Antibodies specifically binding a TAT polypeptide identified herein, as well as other molecules identified by the screening assays disclosed hereinbefore, can be administered for the treatment of various disorders, including cancer, in the form of pharmaceutical compositions.

If the TAT polypeptide is intracellular and whole antibodies are used as inhibitors, internalizing antibodies are preferred. However, lipofections or liposomes can also be used to deliver the antibody, or an antibody fragment, into cells. Where antibody fragments are used, the smallest inhibitory fragment that specifically binds to the binding domain of the target protein is preferred. For example, based upon the variable-region sequences of an antibody, peptide molecules can be designed that retain the ability to bind the target protein sequence. Such peptides can be synthesized chemically and/or produced by recombinant DNA technology. See, e.g., Marasco *et al.*, *Proc. Natl. Acad. Sci. USA*, **90**: 7889-7893 (1993).

The formulation herein may also contain more than one active compound as necessary for the particular indication being treated, preferably those with complementary activities that do not adversely affect each other. Alternatively, or in addition, the composition may comprise an agent that enhances its function, such as, for example, a cytotoxic agent, cytokine, chemotherapeutic agent, or growth-inhibitory agent. Such molecules are suitably present in combination in amounts that are effective for the purpose intended.

The following examples are offered for illustrative purposes only, and are not intended to limit the scope of the present invention in any way.

All patent and literature references cited in the present specification are hereby incorporated by reference in their entirety.

EXAMPLES

Commercially available reagents referred to in the examples were used according to manufacturer's instructions unless otherwise indicated. The source of those cells identified in the following examples, and throughout the specification, by ATCC accession numbers is the American Type Culture Collection, Manassas, VA.

EXAMPLE 1: Analysis of Differential TAT Polypeptide Expression by GEPIS

An expressed sequence tag (EST) DNA database (LIFESEQ®, Incyte Pharmaceuticals, Palo Alto, CA) was searched and interesting EST sequences were identified by GEPIS. Gene expression profiling *in silico* (GEPIS) is a bioinformatics tool developed at Genentech, Inc. that characterizes genes of interest for new cancer therapeutic targets. GEPIS takes advantage of large amounts of EST sequence and library information to determine gene expression profiles. GEPIS is capable of determining the expression profile of a gene based upon its proportional correlation with the number of its occurrences in EST databases, and it works by integrating the LIFESEQ® EST relational database and Genentech proprietary information in a stringent and statistically meaningful way. In this example, GEPIS is used to identify and cross-validate novel tumor antigens, although GEPIS can be configured to perform either very specific analyses or broad screening tasks. For the initial screen, GEPIS is used to identify EST sequences from the LIFESEQ® database that correlate

to expression in a particular tissue or tissues of interest (often a tumor tissue of interest). Then, GEPIS was employed to generate a complete tissue expression profile for the various sequences of interest. Using this type of screening bioinformatics, various TAT polypeptides (and their encoding nucleic acid molecules) were identified as being significantly overexpressed in a particular type of cancer or certain cancers as compared to other cancers and/or normal non-cancerous tissues. The rating of GEPIS hits is based upon several criteria including, for example, tissue specificity, tumor specificity and expression level in normal essential and/or normal proliferating tissues. The following is a list of molecules whose tissue expression profile as determined by GEPIS evidences significant upregulation of expression in a specific tumor or tumors as compared to other tumor(s) and/or normal tissues and optionally relatively low expression in normal essential and/or normal proliferating tissues.

Under each tissue heading shown below is a list of the cDNA sequences that are detectably overexpressed in tumor tissue of the indicated tissue type as compared to normal non-tumor tissue of the same tissue type. As such, the molecules listed below (and the polypeptides they encode) are excellent nucleic acid (and polypeptide) targets for the diagnosis and therapy of cancer in mammals.

15 PERIPHERAL NERVOUS SYSTEM

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| DNA324303 | DNA324573 | DNA324681 | DNA325296 | DNA325405 | DNA325407 |
| DNA325408 | DNA325409 | DNA325410 | DNA325449 | DNA325503 | DNA326083 |
| DNA326231 | DNA188229 | DNA327080 | DNA327081 | DNA327082 | |

20 BRAIN

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|--------------|-----------|-----------|-----------|-----------|-----------|
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| DNA323728 | DNA323729 | DNA323731 | DNA323732 | DNA287173 | DNA151148 |
| DNA323740 | DNA323742 | DNA323743 | DNA323744 | DNA323751 | DNA323753 |
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| 25 DNA323781 | DNA323783 | DNA323785 | DNA323795 | DNA323796 | DNA323797 |
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| 30 DNA323856 | DNA323859 | DNA323863 | DNA323869 | DNA323871 | DNA323874 |
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| DNA323912 | DNA323918 | DNA323921 | DNA323922 | DNA323923 | DNA323924 |
| DNA323925 | DNA323926 | DNA257916 | DNA323927 | DNA323931 | DNA323936 |
| 35 DNA323937 | DNA323938 | DNA323939 | DNA323940 | DNA323942 | DNA226793 |
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ADIPOSE

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WHOLE BLOOD

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5

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| 5 | DNA326047 | DNA326075 | DNA326079 | DNA326099 | DNA326113 |
| | DNA97293 | DNA326122 | DNA326124 | DNA326128 | DNA326129 |
| | DNA326156 | DNA287355 | DNA326187 | DNA326233 | DNA326234 |
| | DNA326254 | DNA326260 | DNA97300 | DNA326273 | DNA326278 |
| | DNA326281 | DNA304715 | DNA326282 | DNA326286 | DNA326292 |
| 10 | DNA326291 | DNA326292 | DNA66475 | DNA326324 | DNA326326 |
| | DNA326364 | DNA326378 | DNA326381 | DNA326396 | DNA326415 |
| | DNA326450 | DNA326451 | DNA326452 | DNA326453 | DNA326454 |
| | DNA326463 | DNA326469 | DNA326499 | DNA287636 | DNA326529 |
| | DNA270315 | DNA326546 | DNA326557 | DNA326559 | DNA326562 |
| 15 | DNA326615 | DNA326620 | DNA227249 | DNA326633 | DNA326634 |
| | DNA326651 | DNA326657 | DNA272347 | DNA326669 | DNA326686 |
| | DNA326688 | DNA326698 | DNA326732 | DNA290260 | DNA326741 |
| | DNA83154 | DNA326756 | DNA326758 | DNA326759 | DNA326769 |
| | DNA287270 | DNA326792 | DNA326796 | DNA326798 | DNA326799 |
| 20 | DNA194701 | DNA103525 | DNA326841 | DNA326862 | DNA326863 |
| | DNA326864 | DNA326866 | DNA326870 | DNA326885 | DNA326886 |
| | DNA326921 | DNA326952 | DNA326969 | DNA326971 | DNA326974 |
| | DNA327016 | DNA327023 | DNA327025 | DNA327029 | DNA273992 |
| | DNA327062 | DNA273254 | DNA327067 | DNA327068 | DNA327073 |
| 25 | DNA327087 | DNA327090 | DNA327092 | DNA276159 | DNA327127 |

STOMACH

| | | | | | |
|-----------|-----------|-----------|-----------|-----------|-----------|
| DNA287173 | DNA323805 | DNA323849 | DNA323864 | DNA323865 | DNA323866 |
| DNA323873 | DNA323884 | DNA323920 | DNA323925 | DNA323934 | DNA323990 |
| 30 | DNA324028 | DNA324029 | DNA324039 | DNA324048 | DNA324065 |
| | DNA227795 | DNA324155 | DNA324179 | DNA324180 | DNA324216 |
| | DNA324244 | DNA324294 | DNA324362 | DNA324364 | DNA324398 |
| | DNA324418 | DNA324471 | DNA324504 | DNA324541 | DNA324552 |
| | DNA324556 | DNA324558 | DNA324624 | DNA324630 | DNA304680 |
| 35 | DNA324769 | DNA324790 | DNA324808 | DNA324850 | DNA225631 |
| | DNA324907 | DNA324908 | DNA324922 | DNA304710 | DNA324962 |
| | | | | | DNA324963 |

| | | | | | | |
|----|-----------|-----------|-----------|-----------|-----------|-----------|
| | DNA324972 | DNA324973 | DNA324982 | DNA324997 | DNA325033 | DNA325074 |
| | DNA325078 | DNA325079 | DNA325104 | DNA325105 | DNA325106 | DNA325148 |
| | DNA325149 | DNA325156 | DNA325157 | DNA89242 | DNA325186 | DNA325191 |
| | DNA325192 | DNA325202 | DNA325224 | DNA325233 | DNA325235 | DNA325236 |
| | DNA325251 | DNA325262 | DNA325268 | DNA325306 | DNA325316 | DNA325318 |
| 5 | DNA325320 | DNA325368 | DNA325418 | DNA97285 | DNA325441 | DNA325442 |
| | DNA325444 | DNA325446 | DNA325474 | DNA325480 | DNA325506 | DNA325534 |
| | DNA325535 | DNA325570 | DNA325601 | DNA225632 | DNA325642 | DNA325644 |
| | DNA325645 | DNA270458 | DNA227092 | DNA325773 | DNA325775 | DNA325776 |
| | DNA325803 | DNA325804 | DNA274058 | DNA325843 | DNA325873 | DNA325941 |
| 10 | DNA325986 | DNA325993 | DNA326019 | DNA287331 | DNA326043 | DNA326133 |
| | DNA326196 | DNA326284 | DNA326311 | DNA326333 | DNA326347 | DNA326397 |
| | DNA326427 | DNA326517 | DNA326603 | DNA326641 | DNA326642 | DNA326698 |
| | DNA326750 | DNA326791 | DNA326846 | DNA326859 | DNA326862 | DNA326863 |
| | DNA304670 | DNA326864 | DNA326865 | DNA326918 | DNA326961 | DNA326977 |
| 15 | DNA326983 | DNA327040 | DNA327042 | DNA327055 | DNA273254 | DNA327099 |
| | DNA327116 | DNA327127 | | | | |

BONE

| | | | | | | |
|----|-----------|-----------|-----------|-----------|-----------|-----------|
| | DNA323765 | DNA323817 | DNA323820 | DNA323829 | DNA323864 | DNA323867 |
| 20 | DNA323869 | DNA323871 | DNA323914 | DNA323947 | DNA323964 | DNA324004 |
| | DNA324009 | DNA324090 | DNA324091 | DNA324092 | DNA324111 | DNA324112 |
| | DNA324154 | DNA324155 | DNA324200 | DNA324201 | DNA324210 | DNA324230 |
| | DNA324293 | DNA226547 | DNA324295 | DNA324326 | DNA324347 | DNA324390 |
| | DNA324417 | DNA324418 | DNA324423 | DNA324437 | DNA324472 | DNA324483 |
| 25 | DNA324488 | DNA324501 | DNA324502 | DNA324503 | DNA324504 | DNA324505 |
| | DNA324512 | DNA324521 | DNA324525 | DNA324541 | DNA324549 | DNA324550 |
| | DNA324551 | DNA324554 | DNA324555 | DNA324556 | DNA324557 | DNA324558 |
| | DNA324575 | DNA324576 | DNA324579 | DNA324595 | DNA324596 | DNA324604 |
| | DNA324613 | DNA324624 | DNA324632 | DNA324641 | DNA324645 | DNA324682 |
| 30 | DNA324687 | DNA324697 | DNA324717 | DNA324720 | DNA324737 | DNA324756 |
| | DNA304661 | DNA324785 | DNA324796 | DNA324797 | DNA150772 | DNA324828 |
| | DNA324829 | DNA324844 | DNA324866 | DNA324902 | DNA324904 | DNA324905 |
| | DNA324906 | DNA324926 | DNA324989 | DNA325015 | DNA325024 | DNA325026 |
| | DNA325027 | DNA325034 | DNA325111 | DNA325116 | DNA131588 | DNA325156 |
| 35 | DNA325157 | DNA325164 | DNA325179 | DNA325182 | DNA325183 | DNA325184 |
| | DNA325202 | DNA325206 | DNA325222 | DNA325229 | DNA325231 | DNA325232 |

| | | | | | | |
|-----------|-----------|-----------|-----------|-----------|-----------|-----------|
| DNA325234 | DNA325236 | DNA325250 | DNA325301 | DNA325303 | DNA325326 | |
| DNA325339 | DNA325340 | DNA325347 | DNA325358 | DNA325395 | DNA325430 | |
| DNA325437 | DNA325451 | DNA325452 | DNA325523 | DNA325558 | DNA325570 | |
| DNA325576 | DNA325601 | DNA325632 | DNA325633 | DNA325731 | DNA325733 | |
| DNA325736 | DNA325762 | DNA325786 | DNA302016 | DNA325789 | DNA325806 | |
| 5 | DNA325810 | DNA325811 | DNA325812 | DNA325843 | DNA325844 | DNA325906 |
| | DNA325908 | DNA325913 | DNA325922 | DNA325935 | DNA325985 | DNA326002 |
| | DNA326041 | DNA326046 | DNA326099 | DNA326233 | DNA326234 | DNA326251 |
| | DNA97300 | DNA304715 | DNA326286 | DNA326289 | DNA326381 | DNA326457 |
| 10 | DNA326580 | DNA326633 | DNA326634 | DNA326635 | DNA326651 | DNA290260 |
| | DNA326796 | DNA326884 | DNA326886 | DNA326974 | DNA326977 | DNA327005 |
| | DNA327025 | DNA327060 | DNA327062 | DNA327067 | DNA327114 | |

EXAMPLE 2: Use of TAT as a hybridization probe

The following method describes use of a nucleotide sequence encoding TAT as a hybridization probe
15 for, i.e., diagnosis of the presence of a tumor in a mammal.

DNA comprising the coding sequence of full-length or mature TAT as disclosed herein can also be employed as a probe to screen for homologous DNAs (such as those encoding naturally-occurring variants of TAT) in human tissue cDNA libraries or human tissue genomic libraries.

Hybridization and washing of filters containing either library DNAs is performed under the following high stringency conditions. Hybridization of radiolabeled TAT-derived probe to the filters is performed in a solution of 50% formamide, 5x SSC, 0.1% SDS, 0.1% sodium pyrophosphate, 50 mM sodium phosphate, pH 6.8, 2x Denhardt's solution, and 10% dextran sulfate at 42°C for 20 hours. Washing of the filters is performed in an aqueous solution of 0.1x SSC and 0.1% SDS at 42°C.

5 DNAs having a desired sequence identity with the DNA encoding full-length native sequence TAT can then be identified using standard techniques known in the art.

EXAMPLE 3: Expression of TAT in *E. coli*

10 This example illustrates preparation of an unglycosylated form of TAT by recombinant expression in *E. coli*.

15 The DNA sequence encoding TAT is initially amplified using selected PCR primers. The primers should contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector. A variety of expression vectors may be employed. An example of a suitable vector is pBR322 (derived from *E. coli*; see Bolivar et al., *Gene*, 2:95 (1977)) which contains genes for ampicillin and tetracycline resistance. The vector is digested with restriction enzyme and dephosphorylated. The PCR amplified sequences are then ligated into the vector. The vector will preferably include sequences which encode for an antibiotic resistance gene, a trp promoter, a polyhis leader (including the first six STII codons, polyhis sequence, and enterokinase cleavage site), the TAT coding region, lambda transcriptional terminator, and an argU gene.

20 The ligation mixture is then used to transform a selected *E. coli* strain using the methods described in Sambrook et al., *supra*. Transformants are identified by their ability to grow on LB plates and antibiotic resistant colonies are then selected. Plasmid DNA can be isolated and confirmed by restriction analysis and DNA sequencing.

25 Selected clones can be grown overnight in liquid culture medium such as LB broth supplemented with antibiotics. The overnight culture may subsequently be used to inoculate a larger scale culture. The cells are then grown to a desired optical density, during which the expression promoter is turned on.

30 After culturing the cells for several more hours, the cells can be harvested by centrifugation. The cell pellet obtained by the centrifugation can be solubilized using various agents known in the art, and the solubilized TAT protein can then be purified using a metal chelating column under conditions that allow tight binding of the protein.

35 TAT may be expressed in *E. coli* in a poly-His tagged form, using the following procedure. The DNA encoding TAT is initially amplified using selected PCR primers. The primers will contain restriction enzyme sites which correspond to the restriction enzyme sites on the selected expression vector, and other useful sequences providing for efficient and reliable translation initiation, rapid purification on a metal chelation column, and proteolytic removal with enterokinase. The PCR-amplified, poly-His tagged sequences are then ligated into an expression vector, which is used to transform an *E. coli* host based on strain 52 (W3110

fuhA(tonA) lon galE rpoHts(htpRts) clpP(lacIq). Transformants are first grown in LB containing 50 mg/ml carbenicillin at 30°C with shaking until an O.D.600 of 3-5 is reached. Cultures are then diluted 50-100 fold into CRAP media (prepared by mixing 3.57 g (NH₄)₂SO₄, 0.71 g sodium citrate•2H₂O, 1.07 g KCl, 5.36 g Difco yeast extract, 5.36 g Sheffield hycase SF in 500 mL water, as well as 110 mM MPOS, pH 7.3, 0.55% (w/v) glucose and 7 mM MgSO₄) and grown for approximately 20-30 hours at 30°C with shaking. Samples are

5 removed to verify expression by SDS-PAGE analysis, and the bulk culture is centrifuged to pellet the cells. Cell pellets are frozen until purification and refolding.

E. coli paste from 0.5 to 1 L fermentations (6-10 g pellets) is resuspended in 10 volumes (w/v) in 7 M guanidine, 20 mM Tris, pH 8 buffer. Solid sodium sulfite and sodium tetrathionate is added to make final concentrations of 0.1M and 0.02 M, respectively, and the solution is stirred overnight at 4°C. This step results in a denatured protein with all cysteine residues blocked by sulfitolization. The solution is centrifuged at 40,000 rpm in a Beckman Ultracentrifuge for 30 min. The supernatant is diluted with 3-5 volumes of metal chelate column buffer (6 M guanidine, 20 mM Tris, pH 7.4) and filtered through 0.22 micron filters to clarify. The clarified extract is loaded onto a 5 ml Qiagen Ni-NTA metal chelate column equilibrated in the metal chelate column buffer. The column is washed with additional buffer containing 50 mM imidazole (Calbiochem, Utrol grade), pH 7.4. The protein is eluted with buffer containing 250 mM imidazole. Fractions containing the desired protein are pooled and stored at 4°C. Protein concentration is estimated by its absorbance at 280 nm using the calculated extinction coefficient based on its amino acid sequence.

The proteins are refolded by diluting the sample slowly into freshly prepared refolding buffer consisting of: 20 mM Tris, pH 8.6, 0.3 M NaCl, 2.5 M urea, 5 mM cysteine, 20 mM glycine and 1 mM EDTA. Refolding volumes are chosen so that the final protein concentration is between 50 to 100 micrograms/ml. The refolding solution is stirred gently at 4°C for 12-36 hours. The refolding reaction is quenched by the addition of TFA to a final concentration of 0.4% (pH of approximately 3). Before further purification of the protein, the solution is filtered through a 0.22 micron filter and acetonitrile is added to 2-10% final concentration. The refolded protein is chromatographed on a Poros R1/H reversed phase column using a mobile buffer of 0.1% TFA with elution with a gradient of acetonitrile from 10 to 80%. Aliquots of fractions with A280 absorbance are analyzed on SDS polyacrylamide gels and fractions containing homogeneous refolded protein are pooled. Generally, the properly refolded species of most proteins are eluted at the lowest concentrations of acetonitrile since those species are the most compact with their hydrophobic interiors shielded from interaction with the reversed phase resin. Aggregated species are usually eluted at higher acetonitrile concentrations. In addition to resolving misfolded forms of proteins from the desired form, the reversed phase step also removes endotoxin from the samples.

Fractions containing the desired folded TAT polypeptide are pooled and the acetonitrile removed using a gentle stream of nitrogen directed at the solution. Proteins are formulated into 20 mM Hepes, pH 6.8 with 0.14 M sodium chloride and 4% mannitol by dialysis or by gel filtration using G25 Superfine (Pharmacia) resins equilibrated in the formulation buffer and sterile filtered.

35 Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using

this technique(s).

EXAMPLE 4: Expression of TAT in mammalian cells

This example illustrates preparation of a potentially glycosylated form of TAT by recombinant expression in mammalian cells.

5 The vector, pRK5 (see EP 307,247, published March 15, 1989), is employed as the expression vector. Optionally, the TAT DNA is ligated into pRK5 with selected restriction enzymes to allow insertion of the TAT DNA using ligation methods such as described in Sambrook et al., *supra*. The resulting vector is called pRK5-TAT.

10 In one embodiment, the selected host cells may be 293 cells. Human 293 cells (ATCC CCL 1573) are grown to confluence in tissue culture plates in medium such as DMEM supplemented with fetal calf serum and optionally, nutrient components and/or antibiotics. About 10 µg pRK5-TAT DNA is mixed with about 1 µg DNA encoding the VA RNA gene [Thimmappaya et al., *Cell*, 31:543 (1982)] and dissolved in 500 µl of 1 mM Tris-HCl, 0.1 mM EDTA, 0.227 M CaCl₂. To this mixture is added, dropwise, 500µl of 50 mM HEPES (pH 7.35), 280 mM NaCl, 1.5 mM NaPO₄, and a precipitate is allowed to form for 10 minutes at 25°C. The precipitate is suspended and added to the 293 cells and allowed to settle for about four hours at 37°C. The culture medium is aspirated off and 2 ml of 20% glycerol in PBS is added for 30 seconds. The 293 cells are then washed with serum free medium, fresh medium is added and the cells are incubated for about 5 days.

15 Approximately 24 hours after the transfections, the culture medium is removed and replaced with culture medium (alone) or culture medium containing 200 µCi/ml ³⁵S-cysteine and 200 µCi/ml ³⁵S-methionine. After a 12 hour incubation, the conditioned medium is collected, concentrated on a spin filter, and loaded onto a 15% SDS gel. The processed gel may be dried and exposed to film for a selected period of time to reveal the presence of TAT polypeptide. The cultures containing transfected cells may undergo further incubation (in serum free medium) and the medium is tested in selected bioassays.

20 In an alternative technique, TAT may be introduced into 293 cells transiently using the dextran sulfate method described by Sompanyrac et al., *Proc. Natl. Acad. Sci.*, 78:7575 (1981). 293 cells are grown to maximal density in a spinner flask and 700 µg pRK5-TAT DNA is added. The cells are first concentrated from the spinner flask by centrifugation and washed with PBS. The DNA-dextran precipitate is incubated on the cell pellet for four hours. The cells are treated with 20% glycerol for 90 seconds, washed with tissue culture medium, and re-introduced into the spinner flask containing tissue culture medium, 5 µg/ml bovine insulin and 0.1 µg/ml bovine transferrin. After about four days, the conditioned media is centrifuged and filtered to remove cells and debris. The sample containing expressed TAT can then be concentrated and purified by any selected method, such as dialysis and/or column chromatography.

25 In another embodiment, TAT can be expressed in CHO cells. The pRK5-TAT can be transfected into CHO cells using known reagents such as CaPO₄ or DEAE-dextran. As described above, the cell cultures can be incubated, and the medium replaced with culture medium (alone) or medium containing a radiolabel such as ³⁵S-methionine. After determining the presence of TAT polypeptide, the culture medium may be replaced

with serum free medium. Preferably, the cultures are incubated for about 6 days, and then the conditioned medium is harvested. The medium containing the expressed TAT can then be concentrated and purified by any selected method.

Epitope-tagged TAT may also be expressed in host CHO cells. The TAT may be subcloned out of the pRK5 vector. The subclone insert can undergo PCR to fuse in frame with a selected epitope tag such as a poly-his tag into a Baculovirus expression vector. The poly-his tagged TAT insert can then be subcloned into a SV40 driven vector containing a selection marker such as DHFR for selection of stable clones. Finally, the CHO cells can be transfected (as described above) with the SV40 driven vector. Labeling may be performed, as described above, to verify expression. The culture medium containing the expressed poly-His tagged TAT can then be concentrated and purified by any selected method, such as by Ni^{2+} -chelate affinity chromatography.

10 TAT may also be expressed in CHO and/or COS cells by a transient expression procedure or in CHO cells by another stable expression procedure.

Stable expression in CHO cells is performed using the following procedure. The proteins are expressed as an IgG construct (immunoadhesin), in which the coding sequences for the soluble forms (e.g. extracellular domains) of the respective proteins are fused to an IgG1 constant region sequence containing the hinge, CH2 and CH2 domains and/or is a poly-His tagged form.

15 Following PCR amplification, the respective DNAs are subcloned in a CHO expression vector using standard techniques as described in Ausubel et al., *Current Protocols of Molecular Biology*, Unit 3.16, John Wiley and Sons (1997). CHO expression vectors are constructed to have compatible restriction sites 5' and 3' of the DNA of interest to allow the convenient shuttling of cDNA's. The vector used expression in CHO cells is as described in Lucas et al., *Nucl. Acids Res.* 24:9 (1774-1779 (1996), and uses the SV40 early promoter/enhancer to drive expression of the cDNA of interest and dihydrofolate reductase (DHFR). DHFR expression permits selection for stable maintenance of the plasmid following transfection.

20 Twelve micrograms of the desired plasmid DNA is introduced into approximately 10 million CHO cells using commercially available transfection reagents Superfect[®] (Qiagen), Dospers[®] or Fugene[®] (Boehringer Mannheim). The cells are grown as described in Lucas et al., *supra*. Approximately 3×10^7 cells are frozen in an ampule for further growth and production as described below.

25 The ampules containing the plasmid DNA are thawed by placement into water bath and mixed by vortexing. The contents are pipetted into a centrifuge tube containing 10 mLs of media and centrifuged at 1000 rpm for 5 minutes. The supernatant is aspirated and the cells are resuspended in 10 mL of selective media (0.2 μm filtered PS20 with 5% 0.2 μm diafiltered fetal bovine serum). The cells are then aliquoted into a 100 mL spinner containing 90 mL of selective media. After 1-2 days, the cells are transferred into a 250 mL spinner filled with 150 mL selective growth medium and incubated at 37°C. After another 2-3 days, 250 mL, 500 mL and 2000 mL spinners are seeded with 3×10^5 cells/mL. The cell media is exchanged with fresh media by centrifugation and resuspension in production medium. Although any suitable CHO media may be employed, a production medium described in U.S. Patent No. 5,122,469, issued June 16, 1992 may actually be used. A 3L production spinner is seeded at 1.2×10^6 cells/mL. On day 0, the cell number pH is determined. On day

1, the spinner is sampled and sparging with filtered air is commenced. On day 2, the spinner is sampled, the temperature shifted to 33°C, and 30 mL of 500 g/L glucose and 0.6 mL of 10% antifoam (e.g., 35% polydimethylsiloxane emulsion, Dow Corning 365 Medical Grade Emulsion) taken. Throughout the production, the pH is adjusted as necessary to keep it at around 7.2. After 10 days, or until the viability dropped below 70%, the cell culture is harvested by centrifugation and filtering through a 0.22 μ m filter. The filtrate was either stored at 4°C or immediately loaded onto columns for purification.

5 For the poly-His tagged constructs, the proteins are purified using a Ni-NTA column (Qiagen). Before purification, imidazole is added to the conditioned media to a concentration of 5 mM. The conditioned media is pumped onto a 6 ml Ni-NTA column equilibrated in 20 mM Hepes, pH 7.4, buffer containing 0.3 M NaCl and 5 mM imidazole at a flow rate of 4-5 ml/min. at 4°C. After loading, the column is washed with additional equilibration buffer and the protein eluted with equilibration buffer containing 0.25 M imidazole. The highly purified protein is subsequently desalted into a storage buffer containing 10 mM Hepes, 0.14 M NaCl and 4% mannitol, pH 6.8, with a 25 ml G25 Superfine (Pharmacia) column and stored at -80°C.

10 Immunoadhesin (Fc-containing) constructs are purified from the conditioned media as follows. The conditioned medium is pumped onto a 5 ml Protein A column (Pharmacia) which had been equilibrated in 20 mM Na phosphate buffer, pH 6.8. After loading, the column is washed extensively with equilibration buffer before elution with 100 mM citric acid, pH 3.5. The eluted protein is immediately neutralized by collecting 1 ml fractions into tubes containing 275 μ L of 1 M Tris buffer, pH 9. The highly purified protein is subsequently desalted into storage buffer as described above for the poly-His tagged proteins. The homogeneity is assessed by SDS polyacrylamide gels and by N-terminal amino acid sequencing by Edman degradation.

15 20 Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 5: Expression of TAT in Yeast

The following method describes recombinant expression of TAT in yeast.

25 First, yeast expression vectors are constructed for intracellular production or secretion of TAT from the ADH2/GAPDH promoter. DNA encoding TAT and the promoter is inserted into suitable restriction enzyme sites in the selected plasmid to direct intracellular expression of TAT. For secretion, DNA encoding TAT can be cloned into the selected plasmid, together with DNA encoding the ADH2/GAPDH promoter, a native TAT signal peptide or other mammalian signal peptide, or, for example, a yeast alpha-factor or invertase secretory signal/leader sequence, and linker sequences (if needed) for expression of TAT.

30 Yeast cells, such as yeast strain AB110, can then be transformed with the expression plasmids described above and cultured in selected fermentation media. The transformed yeast supernatants can be analyzed by precipitation with 10% trichloroacetic acid and separation by SDS-PAGE, followed by staining of the gels with Coomassie Blue stain.

35 Recombinant TAT can subsequently be isolated and purified by removing the yeast cells from the fermentation medium by centrifugation and then concentrating the medium using selected cartridge filters. The

concentrate containing TAT may further be purified using selected column chromatography resins.

Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using this technique(s).

EXAMPLE 6: Expression of TAT in Baculovirus-Infected Insect Cells

5

The following method describes recombinant expression of TAT in Baculovirus-infected insect cells.

The sequence coding for TAT is fused upstream of an epitope tag contained within a baculovirus expression vector. Such epitope tags include poly-his tags and immunoglobulin tags (like Fc regions of IgG). A variety of plasmids may be employed, including plasmids derived from commercially available plasmids such as pVL1393 (Novagen). Briefly, the sequence encoding TAT or the desired portion of the coding sequence of TAT such as the sequence encoding an extracellular domain of a transmembrane protein or the sequence encoding the mature protein if the protein is extracellular is amplified by PCR with primers complementary to the 5' and 3' regions. The 5' primer may incorporate flanking (selected) restriction enzyme sites. The product is then digested with those selected restriction enzymes and subcloned into the expression vector.

10

Recombinant baculovirus is generated by co-transfected the above plasmid and BaculoGold™ virus DNA (Pharmingen) into *Spodoptera frugiperda* ("Sf9") cells (ATCC CRL 1711) using lipofectin (commercially available from GIBCO-BRL). After 4 - 5 days of incubation at 28°C, the released viruses are harvested and used for further amplifications. Viral infection and protein expression are performed as described by O'Reilly et al., Baculovirus expression vectors: A Laboratory Manual, Oxford: Oxford University Press (1994).

15

Expressed poly-his tagged TAT can then be purified, for example, by Ni²⁺-chelate affinity chromatography as follows. Extracts are prepared from recombinant virus-infected Sf9 cells as described by Rupert et al., Nature, 362:175-179 (1993). Briefly, Sf9 cells are washed, resuspended in sonication buffer (25 mL Hepes, pH 7.9; 12.5 mM MgCl₂; 0.1 mM EDTA; 10% glycerol; 0.1% NP-40; 0.4 M KCl), and sonicated twice for 20 seconds on ice. The sonicates are cleared by centrifugation, and the supernatant is diluted 50-fold in loading buffer (50 mM phosphate, 300 mM NaCl, 10% glycerol, pH 7.8) and filtered through a 0.45 μm filter. A Ni²⁺-NTA agarose column (commercially available from Qiagen) is prepared with a bed volume of 5 mL, washed with 25 mL of water and equilibrated with 25 mL of loading buffer. The filtered cell extract is loaded onto the column at 0.5 mL per minute. The column is washed to baseline A₂₈₀ with loading buffer, at which point fraction collection is started. Next, the column is washed with a secondary wash buffer (50 mM phosphate; 300 mM NaCl, 10% glycerol, pH 6.0), which elutes nonspecifically bound protein. After reaching A₂₈₀ baseline again, the column is developed with a 0 to 500 mM Imidazole gradient in the secondary wash buffer. One mL fractions are collected and analyzed by SDS-PAGE and silver staining or Western blot with Ni²⁺-NTA-conjugated to alkaline phosphatase (Qiagen). Fractions containing the eluted His₁₀-tagged TAT are pooled and dialyzed against loading buffer.

20

Alternatively, purification of the IgG tagged (or Fc tagged) TAT can be performed using known chromatography techniques, including for instance, Protein A or protein G column chromatography.

25

Certain of the TAT polypeptides disclosed herein have been successfully expressed and purified using

this technique(s).

EXAMPLE 7: Preparation of Antibodies that Bind TAT

This example illustrates preparation of monoclonal antibodies which can specifically bind TAT.

Techniques for producing the monoclonal antibodies are known in the art and are described, for instance, in Goding, *supra*. Immunogens that may be employed include purified TAT, fusion proteins containing TAT, and cells expressing recombinant TAT on the cell surface. Selection of the immunogen can be made by the skilled artisan without undue experimentation.

Mice, such as Balb/c, are immunized with the TAT immunogen emulsified in complete Freund's adjuvant and injected subcutaneously or intraperitoneally in an amount from 1-100 micrograms. Alternatively, the immunogen is emulsified in MPL-TDM adjuvant (Ribi Immunochemical Research, Hamilton, MT) and injected into the animal's hind foot pads. The immunized mice are then boosted 10 to 12 days later with additional immunogen emulsified in the selected adjuvant. Thereafter, for several weeks, the mice may also be boosted with additional immunization injections. Serum samples may be periodically obtained from the mice by retro-orbital bleeding for testing in ELISA assays to detect anti-TAT antibodies.

After a suitable antibody titer has been detected, the animals "positive" for antibodies can be injected with a final intravenous injection of TAT. Three to four days later, the mice are sacrificed and the spleen cells are harvested. The spleen cells are then fused (using 35% polyethylene glycol) to a selected murine myeloma cell line such as P3X63AgU.1, available from ATCC, No. CRL 1597. The fusions generate hybridoma cells which can then be plated in 96 well tissue culture plates containing HAT (hypoxanthine, aminopterin, and thymidine) medium to inhibit proliferation of non-fused cells, myeloma hybrids, and spleen cell hybrids.

The hybridoma cells will be screened in an ELISA for reactivity against TAT. Determination of "positive" hybridoma cells secreting the desired monoclonal antibodies against TAT is within the skill in the art.

The positive hybridoma cells can be injected intraperitoneally into syngeneic Balb/c mice to produce ascites containing the anti-TAT monoclonal antibodies. Alternatively, the hybridoma cells can be grown in tissue culture flasks or roller bottles. Purification of the monoclonal antibodies produced in the ascites can be accomplished using ammonium sulfate precipitation, followed by gel exclusion chromatography. Alternatively, affinity chromatography based upon binding of antibody to protein A or protein G can be employed.

EXAMPLE 8: Purification of TAT Polypeptides Using Specific Antibodies

Native or recombinant TAT polypeptides may be purified by a variety of standard techniques in the art of protein purification. For example, pro-TAT polypeptide, mature TAT polypeptide, or pre-TAT polypeptide is purified by immunoaffinity chromatography using antibodies specific for the TAT polypeptide of interest. In general, an immunoaffinity column is constructed by covalently coupling the anti-TAT polypeptide antibody to an activated chromatographic resin.

Polyclonal immunoglobulins are prepared from immune sera either by precipitation with ammonium

sulfate or by purification on immobilized Protein A (Pharmacia LKB Biotechnology, Piscataway, N.J.). Likewise, monoclonal antibodies are prepared from mouse ascites fluid by ammonium sulfate precipitation or chromatography on immobilized Protein A. Partially purified immunoglobulin is covalently attached to a chromatographic resin such as CnBr-activated SEPHAROSE™ (Pharmacia LKB Biotechnology). The antibody is coupled to the resin, the resin is blocked, and the derivative resin is washed according to the manufacturer's instructions.

5 Such an immunoaffinity column is utilized in the purification of TAT polypeptide by preparing a fraction from cells containing TAT polypeptide in a soluble form. This preparation is derived by solubilization of the whole cell or of a subcellular fraction obtained via differential centrifugation by the addition of detergent or by other methods well known in the art. Alternatively, soluble TAT polypeptide containing a signal sequence 10 may be secreted in useful quantity into the medium in which the cells are grown.

A soluble TAT polypeptide-containing preparation is passed over the immunoaffinity column, and the column is washed under conditions that allow the preferential absorbance of TAT polypeptide (e.g., high ionic strength buffers in the presence of detergent). Then, the column is eluted under conditions that disrupt 15 antibody/TAT polypeptide binding (e.g., a low pH buffer such as approximately pH 2-3, or a high concentration of a chaotropic such as urea or thiocyanate ion), and TAT polypeptide is collected.

EXAMPLE 9: *In Vitro* Tumor Cell Killing Assay

Mammalian cells expressing the TAT polypeptide of interest may be obtained using standard expression vector and cloning techniques. Alternatively, many tumor cell lines expressing TAT polypeptides of interest 20 are publicly available, for example, through the ATCC and can be routinely identified using standard ELISA or FACS analysis. Anti-TAT polypeptide monoclonal antibodies (and toxin conjugated derivatives thereof) may then be employed in assays to determine the ability of the antibody to kill TAT polypeptide expressing cells *in vitro*.

For example, cells expressing the TAT polypeptide of interest are obtained as described above and 25 plated into 96 well dishes. In one analysis, the antibody/toxin conjugate (or naked antibody) is included throughout the cell incubation for a period of 4 days. In a second independent analysis, the cells are incubated for 1 hour with the antibody/toxin conjugate (or naked antibody) and then washed and incubated in the absence of antibody/toxin conjugate for a period of 4 days. Cell viability is then measured using the CellTiter-Glo 30 Luminescent Cell Viability Assay from Promega (Cat# G7571). Untreated cells serve as a negative control.

EXAMPLE 10: *In Vivo* Tumor Cell Killing Assay

To test the efficacy of conjugated or unconjugated anti-TAT polypeptide monoclonal antibodies, anti-TAT antibody is injected intraperitoneally into nude mice 24 hours prior to receiving tumor promoting cells 35 subcutaneously in the flank. Antibody injections continue twice per week for the remainder of the study. Tumor volume is then measured twice per week.

The foregoing written specification is considered to be sufficient to enable one skilled in the art to

practice the invention. The present invention is not to be limited in scope by the construct deposited, since the deposited embodiment is intended as a single illustration of certain aspects of the invention and any constructs that are functionally equivalent are within the scope of this invention. The deposit of material herein does not constitute an admission that the written description herein contained is inadequate to enable the practice of any aspect of the invention, including the best mode thereof, nor is it to be construed as limiting the scope of the claims to the specific illustrations that it represents. Indeed, various modifications of the invention in addition to those shown and described herein will become apparent to those skilled in the art from the foregoing description and fall within the scope of the appended claims.

WHAT IS CLAIMED IS:

1. Isolated nucleic acid having a nucleotide sequence that has at least 80% nucleic acid sequence identity to:
 - (a) a DNA molecule encoding the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
 - 5 (b) a DNA molecule encoding the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
 - (c) a DNA molecule encoding an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
 - 10 (d) a DNA molecule encoding an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
 - (e) the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
 - (f) the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
 - 15 (g) the complement of (a), (b), (c), (d), (e) or (f).
2. Isolated nucleic acid having:
 - (a) a nucleotide sequence that encodes the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
 - (b) a nucleotide sequence that encodes the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
 - 20 (c) a nucleotide sequence that encodes an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
 - (d) a nucleotide sequence that encodes an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
 - (e) the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
 - 25 (f) the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
 - (g) the complement of (a), (b), (c), (d), (e) or (f).
3. Isolated nucleic acid that hybridizes to:
 - (a) a nucleic acid that encodes the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
 - (b) a nucleic acid that encodes the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
 - (c) a nucleic acid that encodes an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
 - 30 (d) a nucleic acid that encodes an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

- (e) the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (f) the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
- (g) the complement of (a), (b), (c), (d), (e) or (f).

4. The nucleic acid of Claim 3, wherein the hybridization occurs under stringent conditions.

5. The nucleic acid of Claim 3 which is at least about 5 nucleotides in length.

6. An expression vector comprising the nucleic acid of Claim 1, 2 or 3.

7. The expression vector of Claim 6, wherein said nucleic acid is operably linked to control sequences recognized by a host cell transformed with the vector.

8. A host cell comprising the expression vector of Claim 7.

10. The host cell of Claim 8 which is a CHO cell, an *E. coli* cell or a yeast cell.

10. A process for producing a polypeptide comprising culturing the host cell of Claim 8 under conditions suitable for expression of said polypeptide and recovering said polypeptide from the cell culture.

11. An isolated polypeptide having at least 80% amino acid sequence identity to:

- (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
- (c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
- (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
- (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

25. 12. An isolated polypeptide having:

- (a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 30 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;
- (d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
- (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

13. A chimeric polypeptide comprising the polypeptide of Claim 11 or 12 fused to a heterologous polypeptide.

14. The chimeric polypeptide of Claim 13, wherein said heterologous polypeptide is an epitope tag sequence or an Fc region of an immunoglobulin.

15. An isolated antibody that binds to a polypeptide having at least 80% amino acid sequence 5 identity to:

(a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

(b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-10 6355), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

15 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

16. An isolated antibody that binds to a polypeptide having:

(a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

20 (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

25 (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

17. The antibody of Claim 15 or 16 which is a monoclonal antibody.

30 18. The antibody of Claim 15 or 16 which is an antibody fragment.

19. The antibody of Claim 15 or 16 which is a chimeric or a humanized antibody.

20. The antibody of Claim 15 or 16 which is conjugated to a growth inhibitory agent.

21. The antibody of Claim 15 or 16 which is conjugated to a cytotoxic agent.

35 22. The antibody of Claim 21, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

23. The antibody of Claim 21, wherein the cytotoxic agent is a toxin.

24. The antibody of Claim 23, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.
25. The antibody of Claim 23, wherein the toxin is a maytansinoid.
26. The antibody of Claim 15 or 16 which is produced in bacteria.
27. The antibody of Claim 15 or 16 which is produced in CHO cells.
- 5 28. The antibody of Claim 15 or 16 which induces death of a cell to which it binds.
29. The antibody of Claim 15 or 16 which is detectably labeled.
30. An isolated nucleic acid having a nucleotide sequence that encodes the antibody of Claim 15 or 16.
- 10 31. An expression vector comprising the nucleic acid of Claim 30 operably linked to control sequences recognized by a host cell transformed with the vector.
32. A host cell comprising the expression vector of Claim 31.
33. The host cell of Claim 32 which is a CHO cell, an *E. coli* cell or a yeast cell.
34. A process for producing an antibody comprising culturing the host cell of Claim 32 under conditions suitable for expression of said antibody and recovering said antibody from the cell culture.
- 15 35. An isolated oligopeptide that binds to a polypeptide having at least 80% amino acid sequence identity to:
 - (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
 - (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
 - (c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
 - (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
 - (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
 - (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).
- 20 36. An isolated oligopeptide that binds to a polypeptide having:
 - (a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
 - (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
 - (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;
 - (d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 35 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
 - (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355

(SEQ ID NOS:1-6355); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

37. The oligopeptide of Claim 35 or 36 which is conjugated to a growth inhibitory agent.

38. The oligopeptide of Claim 35 or 36 which is conjugated to a cytotoxic agent.

5 39. The oligopeptide of Claim 38, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

40. The oligopeptide of Claim 38, wherein the cytotoxic agent is a toxin.

41. The oligopeptide of Claim 40, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

10 42. The oligopeptide of Claim 40, wherein the toxin is a maytansinoid.

43. The oligopeptide of Claim 35 or 36 which induces death of a cell to which it binds.

44. The oligopeptide of Claim 35 or 36 which is detectably labeled.

45. A TAT binding organic molecule that binds to a polypeptide having at least 80% amino acid sequence identity to:

15 (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

(b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

20 (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

25 46. The organic molecule of Claim 45 that binds to a polypeptide having:

(a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

(b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

30 (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown

in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

47. The organic molecule of Claim 45 or 46 which is conjugated to a growth inhibitory agent.
48. The organic molecule of Claim 45 or 46 which is conjugated to a cytotoxic agent.
49. The organic molecule of Claim 48, wherein the cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
- 5 50. The organic molecule of Claim 48, wherein the cytotoxic agent is a toxin.
51. The organic molecule of Claim 50, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.
52. The organic molecule of Claim 50, wherein the toxin is a maytansinoid.
53. The organic molecule of Claim 45 or 46 which induces death of a cell to which it binds.
- 10 54. The organic molecule of Claim 45 or 46 which is detectably labeled.
55. A composition of matter comprising:
 - (a) the polypeptide of Claim 11;
 - (b) the polypeptide of Claim 12;
 - (c) the chimeric polypeptide of Claim 13;
 - (d) the antibody of Claim 15;
 - (e) the antibody of Claim 16;
 - (f) the oligopeptide of Claim 35;
 - (g) the oligopeptide of Claim 36;
 - (h) the TAT binding organic molecule of Claim 45; or
 - 15 (i) the TAT binding organic molecule of Claim 46; in combination with a carrier.
56. The composition of matter of Claim 55, wherein said carrier is a pharmaceutically acceptable carrier.
57. An article of manufacture comprising:
 - (a) a container; and
 - (b) the composition of matter of Claim 55 contained within said container.
- 25 58. The article of manufacture of Claim 57 further comprising a label affixed to said container, or a package insert included with said container, referring to the use of said composition of matter for the therapeutic treatment of or the diagnostic detection of a cancer.
59. A method of inhibiting the growth of a cell that expresses a protein having at least 80% amino acid sequence identity to:
 - (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
 - (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
 - (c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
 - 30 (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355),
- 35

6355), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising contacting said cell with an antibody, oligopeptide or organic molecule that binds to said protein, the binding of said antibody, oligopeptide or organic molecule to said protein thereby causing an inhibition of growth of said cell.

5 60. The method of Claim 59, wherein said antibody is a monoclonal antibody.

61. The method of Claim 59, wherein said antibody is an antibody fragment.

62. The method of Claim 59, wherein said antibody is a chimeric or a humanized antibody.

10 63. The method of Claim 59, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

64. The method of Claim 59, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

15 65. The method of Claim 64, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

66. The method of Claim 64, wherein the cytotoxic agent is a toxin.

67. The method of Claim 66, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

68. The method of Claim 66, wherein the toxin is a maytansinoid.

20 69. The method of Claim 59, wherein said antibody is produced in bacteria.

70. The method of Claim 59, wherein said antibody is produced in CHO cells.

71. The method of Claim 59, wherein said cell is a cancer cell.

72. The method of Claim 71, wherein said cancer cell is further exposed to radiation treatment or a chemotherapeutic agent.

25 73. The method of Claim 71, wherein said cancer cell is selected from the group consisting of a breast cancer cell, a colorectal cancer cell, a lung cancer cell, an ovarian cancer cell, a central nervous system cancer cell, a liver cancer cell, a bladder cancer cell, a pancreatic cancer cell, a cervical cancer cell, a melanoma cell and a leukemia cell.

30 74. The method of Claim 71, wherein said protein is more abundantly expressed by said cancer cell as compared to a normal cell of the same tissue origin.

75. The method of Claim 59 which causes the death of said cell.

76. The method of Claim 59, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

35 (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures

1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

5 (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

77. A method of therapeutically treating a mammal having a cancerous tumor comprising cells that express a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

10 (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

15 (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising administering to said mammal a 20 therapeutically effective amount of an antibody, oligopeptide or organic molecule that binds to said protein, thereby effectively treating said mammal.

78. The method of Claim 77, wherein said antibody is a monoclonal antibody.

79. The method of Claim 77, wherein said antibody is an antibody fragment.

80. The method of Claim 77, wherein said antibody is a chimeric or a humanized antibody.

25 81. The method of Claim 77, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

82. The method of Claim 77, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

30 83. The method of Claim 82, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

84. The method of Claim 82, wherein the cytotoxic agent is a toxin.

85. The method of Claim 84, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

86. The method of Claim 84, wherein the toxin is a maytansinoid.

35 87. The method of Claim 77, wherein said antibody is produced in bacteria.

88. The method of Claim 77, wherein said antibody is produced in CHO cells.

89. The method of Claim 77, wherein said tumor is further exposed to radiation treatment or a chemotherapeutic agent.

90. The method of Claim 77, wherein said tumor is a breast tumor, a colorectal tumor, a lung tumor, an ovarian tumor, a central nervous system tumor, a liver tumor, a bladder tumor, a pancreatic tumor, or a cervical tumor.

5 91. The method of Claim 77, wherein said protein is more abundantly expressed by the cancerous cells of said tumor as compared to a normal cell of the same tissue origin.

92. The method of Claim 77, wherein said protein has:

(a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

10 (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

15 (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

93. A method of determining the presence of a protein in a sample suspected of containing said protein, wherein said protein has at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

20 (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

25 (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

30 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising exposing said sample to an antibody, oligopeptide or organic molecule that binds to said protein and determining binding of said antibody, oligopeptide or organic molecule to said protein in said sample, wherein binding of the antibody, oligopeptide or organic molecule to said protein is indicative of the presence of said protein in said sample.

35 94. The method of Claim 93, wherein said sample comprises a cell suspected of expressing said protein.

95. The method of Claim 94, wherein said cell is a cancer cell.
96. The method of Claim 93, wherein said antibody, oligopeptide or organic molecule is detectably labeled.

97. The method of Claim 93, wherein said protein has:
(a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
5 (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
(c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;
10 (d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
(f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

15 98. A method of diagnosing the presence of a tumor in a mammal, said method comprising determining the level of expression of a gene encoding a protein having at least 80% amino acid sequence identity to:
(a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
20 (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
(c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
(d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
25 (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
(f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), in a test sample of tissue cells obtained from said mammal and in a control sample of known normal cells of the same tissue origin, wherein a higher level of expression of said protein in the test sample, as compared to the control sample, is indicative of the presence of tumor in the mammal from which the test sample was obtained.

30 99. The method of Claim 98, wherein the step of determining the level of expression of a gene encoding said protein comprises employing an oligonucleotide in an *in situ* hybridization or RT-PCR analysis.
100. The method of Claim 98, wherein the step determining the level of expression of a gene encoding said protein comprises employing an antibody in an immunohistochemistry or Western blot analysis.
35 101. The method of Claim 98, wherein said protein has:

- (a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;
- 5 (d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
- (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown 10 in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

102. A method of diagnosing the presence of a tumor in a mammal, said method comprising contacting a test sample of tissue cells obtained from said mammal with an antibody, oligopeptide or organic molecule that binds to a protein having at least 80% amino acid sequence identity to:

- (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
- (c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
- 20 (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
- (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), and detecting the formation of a complex between said antibody, oligopeptide or organic molecule and said protein in the test sample, wherein the formation of a complex is 25 indicative of the presence of a tumor in said mammal.

103. The method of Claim 102, wherein said antibody, oligopeptide or organic molecule is detectably labeled.

104. The method of Claim 102, wherein said test sample of tissue cells is obtained from an 30 individual suspected of having a cancerous tumor.

105. The method of Claim 102, wherein said protein has:

- (a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- 35 (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;

(d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;

(e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

5 (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

106. A method for treating or preventing a cell proliferative disorder associated with increased expression or activity of a protein having at least 80% amino acid sequence identity to:

(a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

10 (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

15 (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

20 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising administering to a subject in need of such treatment an effective amount of an antagonist of said protein, thereby effectively treating or preventing said cell proliferative disorder.

107. The method of Claim 106, wherein said cell proliferative disorder is cancer.

108. The method of Claim 106, wherein said antagonist is an anti-TAT polypeptide antibody, TAT binding oligopeptide, TAT binding organic molecule or antisense oligonucleotide.

109. A method of binding an antibody, oligopeptide or organic molecule to a cell that expresses a protein having at least 80% amino acid sequence identity to:

25 (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

(b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

30 (c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

(d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

35 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising contacting said cell with an antibody,

oligopeptide or organic molecule that binds to said protein and allowing the binding of the antibody, oligopeptide or organic molecule to said protein to occur, thereby binding said antibody, oligopeptide or organic molecule to said cell.

110. The method of Claim 109, wherein said antibody is a monoclonal antibody.
111. The method of Claim 109, wherein said antibody is an antibody fragment.
- 5 112. The method of Claim 109, wherein said antibody is a chimeric or a humanized antibody.
113. The method of Claim 109, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.
114. The method of Claim 109, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.
- 10 115. The method of Claim 114, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
116. The method of Claim 114, wherein the cytotoxic agent is a toxin.
117. The method of Claim 116, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.
- 15 118. The method of Claim 116, wherein the toxin is a maytansinoid.
119. The method of Claim 109, wherein said antibody is produced in bacteria.
120. The method of Claim 109, wherein said antibody is produced in CHO cells.
121. The method of Claim 109, wherein said cell is a cancer cell.
- 20 122. The method of Claim 121, wherein said cancer cell is further exposed to radiation treatment or a chemotherapeutic agent.
123. The method of Claim 121, wherein said cancer cell is selected from the group consisting of a breast cancer cell, a colorectal cancer cell, a lung cancer cell, an ovarian cancer cell, a central nervous system cancer cell, a liver cancer cell, a bladder cancer cell, a pancreatic cancer cell, a cervical cancer cell, a melanoma cell and a leukemia cell.
- 25 124. The method of Claim 123, wherein said protein is more abundantly expressed by said cancer cell as compared to a normal cell of the same tissue origin.
125. The method of Claim 109 which causes the death of said cell.
126. Use of a nucleic acid as claimed in any of Claims 1 to 5 or 30 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.
- 30 127. Use of a nucleic acid as claimed in any of Claims 1 to 5 or 30 in the preparation of a medicament for treating a tumor.
128. Use of a nucleic acid as claimed in any of Claims 1 to 5 or 30 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.
129. Use of an expression vector as claimed in any of Claims 6, 7 or 31 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.
- 35 130. Use of an expression vector as claimed in any of Claims 6, 7 or 31 in the preparation of

medicament for treating a tumor.

131. Use of an expression vector as claimed in any of Claims 6, 7 or 31 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

132. Use of a host cell as claimed in any of Claims 8, 9, 32, or 33 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.

5 133. Use of a host cell as claimed in any of Claims 8, 9, 32 or 33 in the preparation of a medicament for treating a tumor.

134. Use of a host cell as claimed in any of Claims 8, 9, 32 or 33 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

135. Use of a polypeptide as claimed in any of Claims 11 to 14 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.
136. Use of a polypeptide as claimed in any of Claims 11 to 14 in the preparation of a medicament for treating a tumor.
137. Use of a polypeptide as claimed in any of Claims 11 to 14 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.
138. Use of an antibody as claimed in any of Claims 15 to 29 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.
139. Use of an antibody as claimed in any of Claims 15 to 29 in the preparation of a medicament for treating a tumor.
140. Use of an antibody as claimed in any of Claims 15 to 29 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.
141. Use of an oligopeptide as claimed in any of Claims 35 to 44 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.
142. Use of an oligopeptide as claimed in any of Claims 35 to 44 in the preparation of a medicament for treating a tumor.
143. Use of an oligopeptide as claimed in any of Claims 35 to 44 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.
144. Use of a TAT binding organic molecule as claimed in any of Claims 45 to 54 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.
145. Use of a TAT binding organic molecule as claimed in any of Claims 45 to 54 in the preparation of a medicament for treating a tumor.
146. Use of a TAT binding organic molecule as claimed in any of Claims 45 to 54 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.
147. Use of a composition of matter as claimed in any of Claims 55 or 56 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.
148. Use of a composition of matter as claimed in any of Claims 55 or 56 in the preparation of a medicament for treating a tumor.
149. Use of a composition of matter as claimed in any of Claims 55 or 56 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.
150. Use of an article of manufacture as claimed in any of Claims 57 or 58 in the preparation of a medicament for the therapeutic treatment or diagnostic detection of a cancer.
151. Use of an article of manufacture as claimed in any of Claims 57 or 58 in the preparation of a medicament for treating a tumor.

152. Use of an article of manufacture as claimed in any of Claims 57 or 58 in the preparation of a medicament for treatment or prevention of a cell proliferative disorder.

153. A method for inhibiting the growth of a cell, wherein the growth of said cell is at least in part dependent upon a growth potentiating effect of a protein having at least 80% amino acid sequence identity to:

5 (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);

(b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;

10 (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;

(e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or

15 (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising contacting said protein with an antibody, oligopeptide or organic molecule that binds to said protein, thereby inhibiting the growth of said cell.

154. The method of Claim 153, wherein said cell is a cancer cell.

155. The method of Claim 153, wherein said protein is expressed by said cell.

156. The method of Claim 153, wherein the binding of said antibody, oligopeptide or organic molecule to said protein antagonizes a cell growth-potentiating activity of said protein.

20 157. The method of Claim 153, wherein the binding of said antibody, oligopeptide or organic molecule to said protein induces the death of said cell.

158. The method of Claim 153, wherein said antibody is a monoclonal antibody.

159. The method of Claim 153, wherein said antibody is an antibody fragment.

160. The method of Claim 153, wherein said antibody is a chimeric or a humanized antibody.

25 161. The method of Claim 153, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

162. The method of Claim 153, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

30 163. The method of Claim 162, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.

164. The method of Claim 162, wherein the cytotoxic agent is a toxin.

165. The method of Claim 164, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.

166. The method of Claim 164, wherein the toxin is a maytansinoid.

35 167. The method of Claim 153, wherein said antibody is produced in bacteria.

168. The method of Claim 153, wherein said antibody is produced in CHO cells.

169. The method of Claim 153, wherein said protein has:

- (a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;
- (d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
- (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
- 5 (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

170. A method of therapeutically treating a tumor in a mammal, wherein the growth of said tumor is at least in part dependent upon a growth potentiating effect of a protein having at least 80% amino acid sequence identity to:

- (a) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
- (b) the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
- (c) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide;
- (d) an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide;
- 10 (e) a polypeptide encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
- (f) a polypeptide encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), said method comprising contacting said protein with an antibody, oligopeptide or organic molecule that binds to said protein, thereby effectively treating said tumor.

171. The method of Claim 170, wherein said protein is expressed by cells of said tumor.

172. The method of Claim 170, wherein the binding of said antibody, oligopeptide or organic molecule to said protein antagonizes a cell growth-potentiating activity of said protein.

173. The method of Claim 170, wherein said antibody is a monoclonal antibody.

174. The method of Claim 170, wherein said antibody is an antibody fragment.

175. The method of Claim 170, wherein said antibody is a chimeric or a humanized antibody.

176. The method of Claim 170, wherein said antibody, oligopeptide or organic molecule is conjugated to a growth inhibitory agent.

177. The method of Claim 170, wherein said antibody, oligopeptide or organic molecule is conjugated to a cytotoxic agent.

178. The method of Claim 177, wherein said cytotoxic agent is selected from the group consisting of toxins, antibiotics, radioactive isotopes and nucleolytic enzymes.
179. The method of Claim 177, wherein the cytotoxic agent is a toxin.
180. The method of Claim 179, wherein the toxin is selected from the group consisting of maytansinoid and calicheamicin.
- 5 181. The method of Claim 179, wherein the toxin is a maytansinoid.
182. The method of Claim 170, wherein said antibody is produced in bacteria.
183. The method of Claim 170, wherein said antibody is produced in CHO cells.
184. The method of Claim 170, wherein said protein has:
 - (a) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355);
 - 10 (b) the amino acid sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
 - (c) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355), with its associated signal peptide sequence;
 - (d) an amino acid sequence of an extracellular domain of the polypeptide shown in any one of Figures 15 1-6355 (SEQ ID NOS:1-6355), lacking its associated signal peptide sequence;
 - (e) an amino acid sequence encoded by the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355); or
 - (f) an amino acid sequence encoded by the full-length coding region of the nucleotide sequence shown in any one of Figures 1-6355 (SEQ ID NOS:1-6355).

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FIGURE 1

ATCACATGCCTATCATATAGTAAAACCCAGCCCATGGCCCTAACAGGGGCCCTCAGCCCTCTAACGACCTC
CGGCCTAGCCATGTGATTCACCTCCACTCCACAACCCCTCTCATACTAGGCCTACTAACCAACACACTAACCAT
ATACCAATGATGGCGGATGTAACACGAGAAAGCACATACCAAGGCCACACACCACCTGTCCAGAAAGGCCT
TCGATACGGGATAATCCTATTATTACCTCAGAAGTTTTCTTCGCAGGATTTCTGAGCCTTTACCACTC
CAGCCTAGCTCCCACCCCCCAACTAGGGGACACTGGCCCCAACAGGCATCACCCGCTAAATCCCCTAGAAGT
CCCACTCCTAAACACATCCGTATTACTCGCATCAGGGTATCAATCACCTGAGCTCACCATAGTCTAATAGTCTA
TTTACCCCTCCTACAAGCCTCAGAGTACTTCGAG

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FIGURE 2

TCTAATACCTATTGATCTGCACTTCTCCATCACGCTCAGGTGGGACCATTAGTTGCAGGAAAACAAGCTTA
ACACGCCCACTAATTCTACATTATGGTGAGTTCTATAATTATTTATTATATTACAGTGTAATAATGGAAATA
AAGTGCTAATAATGCAAATGTGCTTACATCTTGGCCAGCTCCTACCTCCCGCAGCCTCTCAGGCCAG
AACTTCTCCAGTCAGCCTACAGACCAAGCTCATGACTCACATGGCTATTAGGCCATACCCATGTCAC
GGCAGCCTCCGCAGATGAGGCTACTGCCTCACACAGCCTCACAGGCACAGCTCCATGTTACAATGGCCTCTT
TAGACCCAGCTCCTGCCTCCAGCCTTCTCCAGGCCCTGAACCTTCTCAAGTCGACCTCACCAAGGCCAGCTC
ATGCTTCTTGAGCCTCTCCAGGCCAGCTCTGCATCTGGTGCCCTCAGGCCAGCCTCTGCCTCCGT
CAGCCTACAGTCCAAAGCTGCCTCACAGCAGATTCTCACGCCAGCATCTACCTCACTGGACCCCTCAG
ACCCAGATGGTGTCTCACTGTGGCATCCTCAGGCGAAGCTCCTGCCCTCGGCAGCCTCTCCAGGCCAGCTCCT
CCTGCCCTCCAGTGGCCTCTTCGGCCAGCCCAGCTCATGCCTCCGGCGGCCCTCCAGGCCAGCTTGTAC
TTTCGGTGGCCTCTGCAGGCCTCGACAAGGCCAGCCTGCCTCCGAAGGCCCTGCACAGGCCAGCCTCTGC
CTCACAGCGGACTCTC

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FIGURE 3

CAAGCTCATGACTACAATGGCTATTAGGCCATACCCCTACGTACGGCAGCCTCCGCAGATGAGCCTACTGC
CTCACAAACAGCCTCCACAGGCACAGCTCCATCGTTACAATGGCCTTTAGACCCAGCTCCTGCCTCCAGCCTT
CTCTCCAGGCTCTGAACCTTCTCAGGTCTCCCTCTGTTCCAAGGCTGGAGTGTAGTAGTGTATCGCAGCTGA
CTGCAGCCTCAACCTCCAGGCTGAAGCGATCCTCCCACCTCAACCTCCCACGTGGCTGAGACTACAGGTGCTTG
CCACTATGCCCAACTAACATTGGAATTTCGTATACGTGGATTCCAGAGGGGTGACAGCGAACACGTGGGACCAT
TCAGTTGCAGGAAAACAAGCTAACACGCCCACTAATTCTACATTATGCTCCTACCTCCGGCAGCCTCTCCAGG
CCCAGAACTTCTCCAGTCAGCCTCTACAGACCAAGCTCATGACTCACAATG

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FIGURE 4

CGTCGGCCCCCGGCCCCCAGCAGCCTCAAAGCCCTGTGACTCACAGCCCTGCTTCCACGGGGGACCTGCCAG
 GACTGGGCATTGGCGGGGCTTCACCTGCAGCTGCCCGCAGGCAGGGGAGGCCTGCTGTGAGAAGGTGCTT
 GGCGCCCTGTGCCGCCCTCGAGGGCCGCTCTCCCTGGCCCTCCCCACTCTCCGCCTACCAACACGCTGCC
 CTGGCACTGGAATTCCGGCGCTGGAGCCTCAGGGCTGCTGTGACTAACATGCCAACGCCGGGCAAGGACTTC
 CTGGCAATTGGCGCTGCTAGATGGCCCGTGCACTCAGGTTGACACAGGTTGGGGCCGGCTGCTGACCAAGT
 GCCGTGCCGGTAGAGCCGGGCACTGGCACCGCCTGGAGCTGTCGGCACTGGCGCCGGGACCCCTCGGTG
 GATGGTGAGACCCCTGTTCTGGCAGAGTCCCAGTGGCACCGACGGCTCAACCTGGACACAGACCTTTGTG
 GGCAGCGTACCCGAGGACCAGGCTGCCGTGGAGCTGCTGGAGCTTGTGAGGCTCTGGCATTGGGCCGGGCTG
 CGCAAGTGCAGCTGCAACACCAGCGCCTGGAGCTGGCATTGGGCCGGGCTGCCACCCGAGGCTCTGGCGT
 GGCAAGTGCAGGGACCACCCCTGCCATGCCAACCCCTGCATGGGGGGCCCATGCCAGAACCTGGAGGCTGGA
 AGGTTCCATTGCCAGTGCCCGCCGGCCGCTGGACCAACCTGTGCCGATGAGAAGAGCCCTGCCAGCCAAC
 CCCTGCCATGGGGCCGCGCCCTGGCGTGTGCTGCCGAGGGTGGTGTCACTGCGAGTGCCCCCTGGCGTGA
 GGCACCTCTGCCAGACAGCCTGGGGCAGGACGGCTCTGGCCCTTCTGGCTGACTTCAACGGCTTCTCCAC
 CTGGAGCTGAGAGGCTGCACACCTTGTACGGGACCTGGGGAGAAGATGGCGCTGGAGGTCGTGTTCTGGCA
 CGAGGCCCCAGCGGCCCTGCTCTACAACGGGAGAACAGCGGACGGCAAGGGGACTTCGTGCTGGCACTG
 CGGGACCGCCGCTGGAGTCCGCTACGACCTGGCAAGGGGAGCGGTACATCAGGAGCAGGAGCCAGTCACC
 CTGGGAGCCTGGACCAGGGTCTACTGGAGCGAACCGCCGAAGGGTGCCTGGCTGTGGCGACGGCCCCGT
 GTGTTGGGGAGTCCCCGGTTCGCACACCGCTCTACAACCTGAAGGAGCCGCTCTACGTAGGGGGCGCTCCGAC
 TTCAGCAAGCTGGCCCCTGCTGCTGCCGTGCTCTGGCTTCGACGGTGCCATCCAGCTGGCTCCCTCGGAGGC
 CGCCAGCTGCTGACCCGGAGCAGTGTGCGGCCAGGTGGACGTACGTCTGGCTGAGGTACCCCTGCCACCCGG
 GCCTCAGGCCACCCCTGCCATGGGGCTCCCTGCCTGGCTCCAGGGAGGCTGCTATGTGTGCTGTGCCCCGG
 GGATTCTCAGGACCGCACTGCGAGAAGGGGCTGGTGGAGAAGTCAGCGGGGACGTGGATACCTGGCTTGTGAC
 GGGCGGACCTTGTGAGTACCTCAACGCTGTGACCGAGAGCGAGAAGGCACTGAGAGCAACCACTTGAAC
 AGCCTGCCACTGAGGCCACGCAAGGGCTGGTGTCTGGAGTGGCAAGGCCACGGAGCGGGAGACTATGTGGCA
 CTGGCCATTGTGGACGGGACCTGCACTGAGCTACAACCTGGCTCCCAGCCGTGGTGTGCGTTCCACCGTG
 CCCGTCAACACCAACCGCTGGTGTGGGTCTGGCACATAGGGAGCAGAGGGAGGTTCCCTGCAGGTGGCAAT
 GAGGCCCTGTGACCGCTCTCCCCGCTGGCGCCACGCACTGGACACTGATGGAGCCCTGTGGCTTGGGACGTG
 CTGGCGAGCTGCCCTGGGCCAGCACTGCCAACGGCTACGGCACAGGCTTGTGGCTGCTTGGGCCCTGCCACCCCA
 TGAGCTGGCACCAAGAGCCCCGCGCCGCTGTAATTATTTCTATTTGTAAACTGTTGCTTTTGATATGATT
 TTCTTGCTGAGTGTGGCGGAGGGACTGCTGGCCGCCCTCCCTGGCTCAGGCAGCCGTGCTGCAAGACAGA
 CCTAGTGGCAGGGATGGACAGGGCAGGGTGGCAGCGTGGAGGGCTGGCTGGATGGCAGCCTCAGGACACACAC
 CCCTGCCCTCAAGGTGCTGAGCCCCCGCCTGCACTGCCCTGCCACGGTGTCCCGCCGGAAAGCAGCCCCGG
 CTCCCTGAATCACCTCGCTCCGTCAAGCGGGACTCGTGTCCCAGAGAGGAAGGGGCTGCTGAGGTCTGATGGGG
 CTTCTCCGGGTGACCCACAGGGCTTCAAGCCCCATTGAGCTGCTCTTCTGTGTGCTCTGGGCC
 CTGCGCTGGCCATGCGCAAAACTGACTTCAAAACATGTTACTGCTGGCACAGCTCTGCGTTGCTCCCG
 TGCTGCGCTGCGCCAGGGCAGGCTGCTGAGGAGCAGAGGCCAGACCAAGGGCCGATCTGGTGTCTGACCCCTCAG
 CTGGCCCTGCCAGCCACCCCTGGACATGACCGTATCCCTGCCACACCCAGGGCTGCCAGGGCTATCGAGA
 GGAGCTACTGTGGGATGGGTTGACCTCTGCCGCTGCCCTGGGTATCTGGGCTGGCATGGCTGTGTTCTCA
 TGTGTTGATTTATTGACCCCTGGAGTGGTGGGTCTCATCTTCCCATCTGCCCTGAGAGCGGCTGAGGGCTGC
 CTCACGTGAAATCCTCCCCACAGCGTCAGTGAAAGTCGTCTGTGACTAACATGCCAACGCCAGCCAGTGTCT
 GACCAAGGTCAAGGGCAGGTGCAGAGGTGGCAGGGATGGCTCCGAAGCCAGAAATGCCCTAAACTGCAACGTCC
 CGTCCCTCCCCACCCCCATCCCATCCCCACCCCCAGGCCAGTCCTAGGAGCAGGACCCGATGAAG
 CGGGCGGGGGTGGGTGGGTGCGCTGTTACTAATGTTCTGTGCTGAAATCGCTGTGAAATAAGTCT
 GAAAAACTTT

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FIGURE 5

MLNSSLMRITLRNLEEEFVCVEDKPGTHFTPVPPTPPDACRGMLCGFGAVCEPNAEGPGRASCVCKKSPCP SVVA
PVCGSDASTYSNECELQRAQCSQQRRIRLLSRGPGCSRDPCSNTCSFGSTCARSADGLTASCLCPATCRGAPEG
TVCGSDGADYPGECQLLRRACARQENVFKFDGPGCDPCQGALPDP SRSCRVNPRTRPEMLLRPESCPARQAPVC
GDDGVTYENDCVMGRSGAARGLLLQKVSGQCQGRDQCPEPCRFNAVCLSRRGRPRCSCDRVTCDGAYRPVCAQD
GRTYDSDCWRQQAECRQQRAIPSKHQGPCDQAPSPCLGVQCAFATCAVKNGQAACECLQACSSLYDPVCGSDGV
TYGSACELEATACTLGREIQVARKGPCDRCGQCRFGALCEAETGRVCVPSECVALAQPVCGSDGHTYSECMHV
HACTHQISLHVVASAGPCETCGDAVCAFGAVCSAGQCVCPRCEHPPPGPVCSDGVTVGSACELREAACLQQTQIE
EARAGPCEAQECGGSGSGGEDGDCEQELCRQGGIWDEDSEDGPCVCFSCQSVPGSPVCGSDGVTVSTECELK
KARCESQRGLYVAAQGACRGPTFAPLPPVAPLHCAQTPYGCCQDNITAARGVGLAGCPSACQCNPHGSYGGTCDF
ATGQCSCRPVGGLRCDRCEPGFWNFRGIVTDGRSGCTPCSCDPQGAVRDDCEQMTGLCSCKPGVAGPKCGQCPD
GRALGPAGCEADASAPATCAEMRCEFGARCVESGSAHCVCPLTCPEANATKVGSDGVTVGNECQLKTIACRQ
GLQISIQLGPGCQEAVAPSTHTSASVTTPGLLSQALPAPPGLAPSSTAHSQTTPPPSSRPTTASVPR
TTVWPVLTVPPTAPSPAPSLVASAFGESGSTDGSSDEELSGDQEASGGGSGGLEPLEGSSVATPGPPVERASCYN
SALGCCSDGKTPSLDAEGSNCPATKVFQGVLELEGVEGQELFYTPEMADPKSELFGETARSIESTLDDLFRNSDV
KKDFRSVRLRDLGPGKSVRAIVDHFDPTTAFRAPDVARALLRQIQVSRRRSILGVRRPLQEHVRFMDFDWFPAPI
TGATSGAIAAGATARATTASRLPSSAVTPRAPHPSHTSQPVAKTTAAPTTRRPTTAPSRVPGRRPPAPQOPPKP
CDSQPCFHGGTCQDWALGGGFTCSCPAGRGGAVERCEKVLGAPVPAFEGRSFLAFTPRLRAYHTLRLALEFRALEPQG
LLLYNGNARGKDFLALALLDGRVQLRFDTGSGPAVLTSAVPVEPGQWHRLELSRHWRRTLSVDGETPVLGESPS
GTDGLNLDTDLFVGGVPEDQAAVALERTFGAGLRCIIRLLDVNNQRLELGIIGPQAATRGSGVGKCGDHPCCLPNP
CHGGAPCQNLEAGRHFHCQCPPGRVGPTCADEKSPCQPNPCHGAAPCRVLPEGGAQCECPLGREGTFCQTASQDG
SGPFLADFNFGFSHIELRGLHTFARDLGEKMALEVVFILARGPSGLLLYNGQKTDGKDFVSIALRDRRLEFRYDLG
KGAAVIRSREPVTLGAWTRVSLERNGRKGALRGDGPRVLGESPVHTVNLKEPLYVGGAPDFSKLARAASVSS
GFDGAIQLVSLGGRQLLTPEHVLRQDVTSFAGHPCTRASGHPCNGASCVPREAAVCLCPGGFSGPHCEKGLV
EKSAGDVDTLAFDGRTFVEYLNNAVTESEKALQSNHFELSRLTEATQGLVLWSKGATERADYVALAIVDGLHLQSY
NLGSQPVVLRSTVPVNTNRWLRVVAHREQREGSLQVGNEAPVTGSSPLGATQLTDGALWLGLPELPVGPALPK
AYGTGFVGCLRDUVGRHPLHLEDAVTKPELRPCPTB

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FIGURE 6

ACAGAGACCCCGAGTTCTACAAGTTCTGCAGGAGAATGACCAGAGCCTGCTAAACTCAGCGACTCGGACAGCT
CTGAGGAGGAAGAGGGGCCGTTCCACTCCCTGCCAGATGTGCTGGAGGAAGCCAGTGGAGGAGGATGGAGCGG
AGGAAGGAGAAGATGGGACAGAGTCCCCAGAGGGCTGAAGGGGAAGAAGAATTCTGTTCTGTGACCGTCGCCA
TGGTGAGAGATGGAAGCAGGAGCAAAGCAACGCCTCACTCCAAAGCTGTTCCATGAAGTGGTACAGGCCTCC
GAGCAGCTGTGGCCACCACCCGAGGGGACCAAGGAAAGTGTGAGGCCAACAAATTCCAGGTACGGACAGTGTG
CATTCAATGCTCTGTTACCTCTGCATCAGAGACCTATTGGCTGTCTCCAGAAGCTGCTGTTGGAAAGGTGG
CAAAGGATAGCAGCAGGATGCTGCAGCCGTCAGCAGCCGCTCTGGGGAAAGCTTCGTGTTGGACATCAAGGCTT
ACCTGGGCTCGGCCATACAGCTGGTGTCCCTGTGTCGGAGACGACGGTGTGGCGCGTGCTGCCGACATCA
GCGTGCTGGTGCCTGCTTCCTGACCTTCCCAAGCAGTGCCTGCTCAAGAGAATGGTATGCTATGGA
GCACTGGGAAGAGTCTCTGCGGGTGTGGCTTCTGGTCTCAGCAGAGTCTGCCGACAAGAAGGACACTT
TCCTTGGCCCCGTCCTCAAGCAAATGTACATCACGTATGTGAGGAACGTCAAGTTCACCTCGCCTGGTGCCTCC
CCTTCATCAGTTCATGCAGTGGACCTTGACGGAGCTGCTGGCCCTGGAGCCGGTGTGGCTACCAGCACGCCT
TCCTCTACATCCGCCAGCTGCCATACACCTCGCAACGCCATGACCAACTCGCAAGAAGGAAACATACAGTCTG
TGTACAACCTGGCAGTATGTGCACTGCCCTTCCCTGTGGTGCCTGAGCAGTGCAGGCCCCAGCGAAGGCC
TCCAGCCCTGGCTACCCCTGCCAAGTCATCATGGCTGTATCAAGCTCATCCCCACTGCCGCTTCTACC
CGCTGCGAATGCACTGCATCCGTGCCCTGACGCTGCTCGGGAGCTCGGGGCCCTCATCCGGTGTGCCCT
TCATCCTGGAGATGTTCCAGCAGGTGCACTCAACAGGAAGCCAGGGCGCATGAGCTCAAGCCATCAACTTCT
CCGTGATCCTGAAGCTGTCATGTCAACCTGCAGGAGAAGCGTACCGGGACGGCTGGTGGAGCAGCTGTACG
ACCTCACCTGGAGTACCTGCACAGCCAGGGCACACTGCATCGGCTCCCGGAGCTGGTGTGCTGCCCTGTTCTGC
AGCTGAAGTCGTTCCCTCCGGAGTGCAAGGTGGCCAACACTGCGGCAAGGTGCAAGCAGTGTGTTGGAAAGGTT
AGGAGAAACTCGGCATACATCTGAGCCGCCAGAGGGTTCTCGCGTCTCTGAGCAGCAGGAGCTGGAAG
CTGGGAGAAGCTGACCCGGGAAGAGGGACACCCCTGACCTGTACTACAGCCACTGGCGAAGCTGCGTGACC
GGGAGATCCAGCTGGAGATCAGTGGCAAAGAGCGGCTGGAAGACCTGAACCTCCCTGAGATCAAACGAAGGAAGA
TGGCTGACAGGAAGGATGAGGACAGGAAGCAATTAAAGACCTTTGACCTGAACAGCTCTGAAGAGGACGACA
CCGAGGGATTCTCGGAGAGAGGGATACTGAGGCCCTGAGCACTCGGCACTGGCGTCTGAGCAGCAGGAGCTGGAAG
AGGAGGAGGGCGAGGAGGACAGCAGCAACTCGGAGGATGGAGACCCAGACGCAAGGGCGGGCTGGCCCTGGG
AGCTGCAGCAGCTGGCCAGGGCGGAGGACAGCAGCTGGAGGATCTGCAGCTCTCAGAGGACGACTGAGGCA
CATCTGGGGGCTGTAGGGCTGCCGGCTGGTGGCAGTGTGTTCCACCTCCCTGGCAGTCAGGCCTAGAGGCT
GGCGTCTGTGCACTGGGGAGGCAGTAGACACGGGACAGGCTTATTATTATTTCAGCATGAAAGACCAA
CGTATCGAGAGCTGGCTGGCTGGCTGGCTGCTGAAGCCCCACAGCTGTGGCTGCTGAAGTCAGCTC
CGCGGGGGAGCTGACCTGACGTCAGCAGACCGAGACCAAGTCCAGGGGAGGCCCTGCAGGCCCTGGC
CCCTCCACACCTCTGCCCTCGTGCAGACCTCGTCCATCTGCACCCAGGCTCTGCCCTACTCCCCAAGTC
TTGAAAATTGTTCTTCCCTTGAACTACATTTCATTAAATTTGTTGCATCCGAAACCGAAAGA
AATAAGCGGTGGGAGGCAGGGCATTGTGTTG

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FIGURE 7

MAAAGSRKRRLAELTVDEFLASGFDESESESESENSPQAETREAREAARSPDKPGGSPSASRRKGRASEHKDQLSR
LKDRDPFIFYKFLQENDQSLLNFSDSDSSEEEEGPFHSLPDVLEEASEEEDGAEEGEDGDRVPRGLKGKKNSVPVT
VAMVERWKQAQKQLTPKLFHEVVQAFRAAVATTRGDQESAEANKFQVTDSAAFNALVFCIRDLIGCLQKLLFG
KVAKDSSRMLQPSSPLWGKLRVDIKAYLGSAIQLVSCLSETTVIAAVLRHISVLVPCFLTFPKQCRMILLKRMVI
VWSTGEESLRVLAFLVLSRVCRHKDTFLGPVLKQMYITYVRNCKFTSPGALPFISFMQWTLTELLALEPGVAYQ
HAFLYIRQLAIHLRNAMTRKKETYQSVYNWQYVHCLFLWCRVLSTAGPSEALQPLVYPLAQVIIGCIKLIPTAR
FYPLRMHCIRALTLLSGSSGAFIPVLPFILEMFQQVDFNRKPGRMSSKPINFSVILKLSNVNLQEKAYRDGLVEQ
LYDLTLEYLHSQAHCIGFPELVLPVVLQLKSFLRECKVANYCRQVQQLLGKVQENSAYICSRQRVSGVSEQQA
VEAWEKLTREEGTPLTLYYSHWRKLRDREIQLIEISGKERLEDLNFPPEIKRRKMADRKEDEDRKQFKDLFDLNSSEE
DDTEGFSERGILRPLSTRHGVEDDEEDEEEGEEDSSNSEDGDPDAEAGLAPGELQQLAQGPEDELEDLQLSEDD